Effect of formoterol fumarate treatment on exercise-induced bronchoconstriction in children

David Pearlman, MD*; Henry Milgrom, MD†; Denise Till, MSc‡; and Barbara Ziehmer, MD§

Background: Exercise-induced bronchoconstriction (EIB) is common, particularly in children.

Objectives: To compare the protective effect of single doses of formoterol fumarate via Aerolizer with placebo and albuterol in children with EIB.

Methods: In this randomized, double-blind, double-dummy, crossover trial, 23 children (aged 4–11 years) received formoterol, 12 or 24 μg; albuterol, 180 μg; or placebo at 4 separate visits. Protection against EIB was evaluated as the maximum percentage decrease in forced expiratory volume in 1 second (FEV_1) from the preexercise value after exercise challenge tests (6-minute treadmill) conducted 15 minutes and 4, 8, and 12 hours after administration of the dose.

Results: The maximum percentage decrease in FEV_1 after the 4-hour exercise test (primary efficacy variable) was significantly less for formoterol, 12 and 24 μg, vs placebo ($P < .001$ for both) or albuterol ($P = .016$ and .010, respectively); albuterol was not significantly different from placebo. Formoterol, 12 and 24 μg, differed from placebo at 8 hours ($P = .002$ and .001, respectively), with a smaller difference between albuterol and placebo ($P = .045$). Rescue medication use and a high dropout rate may have biased treatment differences at later time points. Protection against EIB (<20% maximum decrease in FEV_1) across all time points was observed for 17 (77%) of 22 and 17 (74%) of 23 children with formoterol, 12 and 24 μg, respectively, compared with 8 (35%) of 23 with albuterol and 6 (27%) of 22 with placebo.

Conclusions: Single doses of formoterol, 12 or 24 μg, are effective in protecting against EIB in children, affording a statistically significantly greater protective effect than placebo or albuterol.

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INTRODUCTION

Exercise is a well-known trigger of asthma symptoms in patients of all ages. Exercise-induced bronchoconstriction (EIB) is particularly common in children and young adults,[1] probably because of their high level of physical activity. As such, EIB management is crucial so that children with asthma can participate more fully in sporting activities. Exercise-induced bronchoconstriction may be reduced or controlled by anti-inflammatory therapy with an inhaled corticosteroid.[2] For patients who still experience EIB despite such treatment or whose EIB is the only manifestation of their asthma, current asthma management guidelines recommend administration of a rapid-acting inhaled β_2-agonist, such as albuterol, immediately before exertion.[3] Albuterol offers rapid protection from EIB, but this protection wanes within approximately 4 hours.[4] Formoterol fumarate has a similar onset of protective effect and can protect against EIB for up to 12 hours.[5,6] The effectiveness of formoterol in protecting against EIB has been demonstrated in previous studies[7,8] in children using formoterol administered via a pressurized metered-dose inhaler (MDI) and in studies[5,6] in adolescents and adults in which formoterol was given via a single-dose dry powder inhaler. We, therefore, sought to investigate the effectiveness of formoterol fumarate given via the same single-dose dry powder inhaler (Foradil Aerolizer; Novartis Pharmaceuticals Corp) also in protecting against EIB in children.

The Aerolizer has features that are particularly suited to ease of use by children,[9] who may be more prone than adults to problems with inadequate dosing via inhaler devices.[10] The device has various feedback mechanisms to show that the dose has been taken (eg, the empty capsule), and the low resistance of the device means that the drug is successfully delivered at inspiratory flows that can be achieved by most patients, including young children.[11,12] The trial was designed to evaluate the protective effect and the onset and duration of protection against EIB in children of formoterol, 12- or 24-μg doses, via Aerolizer compared with placebo and albuterol, 180 μg, via pressurized MDI.

METHODS

Patients

The study enrolled children aged 4 to 11 years with demonstrable EIB (≥20% decrease in forced expiratory volume in 1 second [FEV_1] within 30 minutes of starting an exercise challenge test). Their baseline FEV_1 measured at screening (visit 1) was at least 70% of predicted and was not to vary by more than 20% when measured again at visit 2 (scheduled 5 days later). Patients were ineligible if they had any malignancy, cardiovascular disease, or any other serious medical history, including emergency treatment for asthma in the 3 months before visit 2 or a respiratory tract infection within 1 month of visit 2.

* Colorado Allergy and Asthma Centers PC, Denver, Colorado.
† National Jewish Medical and Research Center, Denver, Colorado.
‡ Novartis Horsham Research Centre, Horsham, England.
§ Novartis Pharmaceuticals Corp, East Hanover, New Jersey.
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Intermittent, on-demand use of albuterol via pressurized MDI was allowed as rescue medication. Inhaled or nasal corticosteroids were allowed concomitantly if patients were receiving stable doses, ie, had not started treatment or changed dose, schedule, formulation, or product in the 2 weeks (for nasal corticosteroids) or 1 month (for inhaled corticosteroids) before randomization. Allergen immunotherapy was allowed if treatment was started more than 3 months before randomization. Patients were withdrawn if these treatments changed during the study. Medications that were not permitted included oral, parenteral, and nebulized short- and long-acting β_2-agonists; theophyllines; parenteral or oral corticosteroids; cromones; antileukotriene drugs; and anticholinergics. Patients were allowed to take short-acting formulations of the antihistamines chlorpheniramine maleate and diphenhydramine hydrochloride, but not during the 24 hours before any trial visit.

Study Design and Procedure

This randomized, double-blind, double-dummy, 4-way crossover trial was conducted at 2 medical centers (Colorado Allergy and Asthma Centers PC and National Jewish Medical and Research Center). Treatments were supplied via 2 devices: the Aerolizer dry powder inhaler (formoterol, 12 and 24 μg, or placebo) or a pressurized MDI (albuterol, 180 μg, or placebo). A spacer device was not used with the MDI. The treatment sequence was randomly allocated, and all the visits were separated by at least 3 days (Table 1). Inhalation techniques were taught to the children, and their ability to use the inhaler devices correctly was reviewed before each administration of study medication.

Randomization was achieved using a computer-generated code supplied by the sponsor (Novartis Pharmaceuticals Corp), using a validated system that automated the random assignment of treatment sequence to randomization numbers. Double blinding was achieved using a double-dummy technique, whereby at each visit patients inhaled the dry powder contents of 2 capsules from the Aerolizer (capsules contained formoterol, 12 μg, or placebo) and 2 inhalations from the pressurized MDI (of albuterol, 90 μg per puff, or placebo). Patients and investigators remained blinded to treatment sequence, and personnel from the study center or from the sponsor who were involved in the monitoring or conduct of the trial were blinded to the trial drug codes, except in the case of an emergency. Trial drug codes were not available to these personnel until after the trial was completed, and the blinded data were reviewed and locked electronically to prevent further changes.

Exercise testing was conducted at ambient room temperature (20°C–25°C) and in a dry environment. Patients exercised for 6 minutes on a treadmill, and the intensity of the exercise was monitored by pulse rate, which was to reach 80% to 90% of each individual's predicted maximum; 2 exercise tests were performed 4 hours apart at the first study visit (baseline). At subsequent visits, 4 exercise tests were conducted at 15 ($\pm$5) minutes and at 4, 8, and 12 hours ($\pm$15 minutes) after dose administration. The earliest time point was chosen to allow comparison of onset of protective effect, and the later time points were chosen to evaluate duration of effect. An interval of at least 3 hours between tests was necessary to minimize the refractory response that may occur as a carryover effect from previous exercise.[13] Albuterol pressurized MDI was provided as rescue medication for patients who became symptomatic during or after exercise testing. Time and dose of rescue medication were recorded, and patients could continue their scheduled study procedures.

At the screening visit, a complete medical history was obtained, and patients underwent a physical examination, including vital signs. Electrocardiograms (ECGs) were recorded before and after a first exercise test. The FEV_1 was recorded before and after the first exercise test and before and after a second test 4 hours later to confirm eligibility. At each subsequent visit, vital signs were measured before and after each exercise test, and ECGs were recorded 2 hours after dose administration. The ECGs, including an evaluation of corrected QT interval (QTc) measurements, which could be affected by this class of study drug, were performed to further evaluate cardiac safety. A change in QTc of more than 60 milliseconds or prolongation beyond 460 milliseconds was considered clinically relevant. Clinical laboratory tests (hematology, blood chemistry, and urinalysis) were performed at screening and at the last study visit as part of the standard evaluation of safety and care of patients during the study. Adverse events were recorded at each visit.

Written informed consent was provided by the children's parents or legal guardians before any study-related procedures. The study was performed in accordance with good clinical practice and the directives of the Declaration of Helsinki, the rules governing medicinal products in the European Community (Directive 91/507/EEC), and US 21 Code of Federal Regula-

Table 1. Randomization to Double-Blind Treatment Sequence at Screening (Visit 1)

Visit*	Treatment sequence			
	A	B	C	D
2	Formoterol, 12 μg	Formoterol, 24 μg	Albuterol, 180 μg	Placebo
3	Formoterol, 24 μg	Placebo	Formoterol, 12 μg	Albuterol, 180 μg
4	Albuterol, 180 μg	Formoterol, 12 μg	Placebo	Formoterol, 24 μg
5	Placebo	Albuterol, 180 μg	Formoterol, 24 μg	Formoterol, 12 μg

* Visits were scheduled at least 3 days apart to allow for washout.

tions dealing with clinical studies concerning informed patient consent and institutional review board approval.

Efficacy Evaluations

The primary efficacy variable was the maximum percentage decrease in FEV_1 from the preexercise value to the postexercise value recorded at the 4-hour exercise challenge test. If patients could not complete the exercise test or used rescue albuterol, the value from the previous exercise test was used for analysis (last observation carried forward [LOCF]). Secondary assessments included the maximum percentage decrease in FEV_1 for the 15-minute, 8-hour, and 12-hour exercise challenge tests. The maximum percentage decrease in FEV_1 was also analyzed as the change from the pretreatment (as opposed to preexercise) value.

Spirometry was performed according to the standards of Polgar and Promadhat.[13] To reduce the diurnal variability of observations in clinical efficacy measurements, baseline spirometry was conducted between 6 and 9 AM at each visit. When possible, the same qualified person evaluated a given patient at the same time of day at each visit throughout the trial. This person coached the patient in the performance of spirometry and exercise. Pulmonary function testing was conducted in duplicate. The recorded FEV_1 was obtained from the spirometry maneuver yielding the largest FEV_1. If a patient's baseline FEV_1 at any treatment visit was lower than 60% of predicted, the visit was rescheduled. During a given visit day, if the preexercise test FEV_1 was less than 60% of predicted, the challenge test was not conducted. Spirometry was performed before exercise and 2, 5, 10, 15, 20, 30, 45, and 60 minutes after each exercise challenge test.

Statistical Analysis

Efficacy hypotheses were tested at the 5% level using an analysis of covariance (ANCOVA) model, including sequence, patient (nested in sequence), treatment, period, and the corresponding pretreatment baseline as a covariate. For the primary analysis, the null hypothesis that there was no difference between treatment with formoterol vs placebo with respect to the maximum percentage decrease in FEV_1 was tested for each dose. The analyses were repeated including an effect for carryover. In addition, comparisons of the 2 doses of formoterol with placebo were tested with adjustment for multiplicity using the Hochberg method, thereby preserving the overall .05 significance level.[14] Similarly, adjustments for multiple testing were made for the comparisons of the 2 doses of formoterol with albuterol. The maximum percentage decreases in FEV_1 were analyzed with and without LOCF. The ANCOVA was performed for the 15-minute, 4-hour, 8-hour, and 12-hour postdose time points using the intention-to-treat (ITT) population (randomized patients who took at least 2 different types of study drug and performed at least 1 postdose exercise challenge test after each of the 2 study drugs). The maximum percentage decrease in FEV_1 was considered invalid if any FEV_1 value was measured within 6 hours of rescue medication use. In these cases, the maximum percentage decrease in FEV_1 at the previous exercise test (same visit) was carried forward for analysis.

Safety data are summarized by treatment. All safety analyses were based on the population of randomized patients who took at least 1 dose of study drug, which in the present study was identical to the ITT population. It was estimated that 20 completed patients were required for statistical analysis of the primary variable after each completed exercise challenge test. This was based on variability observed in similar formoterol trials[5,6] performed to study the protective effect on EIB in adolescent and adult patients. It was considered important to detect a difference in maximum percentage decrease in FEV_1 of 16% between formoterol and placebo assuming an SD of 14%. Using a 2-sided test at the .05 significance level, it was estimated that 5 patients per sequence were required to provide 90% power, giving a total of 20 patients.

RESULTS

Demographics

Twenty-three children were enrolled; 21 received all 4 medications and completed their treatment sequences (formoterol, 12 μg, n = 22; formoterol, 24 μg, n = 23; albuterol, n = 23; and placebo, n = 22). The remaining 2 patients received 3 treatments. Baseline demographic and background characteristics of the ITT population are given in Table 2. Three children (13%) were younger than 6 years, 5 (22%) were 6 to 8 years old, and 15 (65%) were 9 to 11 years old. Asthma therapy comprised inhaled albuterol on demand (all patients) and inhaled corticosteroids (5 patients; 22%). Patient recruitment started in June 2001, and the last patient completed the study in November 2001.

Primary Efficacy Analysis

The maximum percentage decrease in FEV_1 (with LOCF) from preexercise values at the 4-hour postdose exercise test was significantly smaller for both doses of formoterol compared with placebo (formoterol, 12 and 24 μg, $P < .001$ for both) and albuterol (formoterol, 12 μg, $P = .016$; formoterol, 24 μg, $P = .010$) (Fig 1). These differences were significant when tested without adjustment at the .05 level and when tested again after adjusting for multiplicity according to the Hochberg method. The differences between albuterol and placebo ($P = .255$) and between the 2 formoterol doses ($P = .871$) were not significant.

The results for the primary efficacy variable were similar, with statistically significant treatment differences when LOCF was not applied (results not shown). When the primary analysis was repeated to include carryover in the ANCOVA model, the findings were again similar to those seen in the original analysis, with statistically significant treatment difference estimates for the same treatment comparisons (results not shown).

To test for any possible impact of any difficulties recording spirometry for the youngest children, analysis of the primary efficacy variable (the maximum percentage decrease in FEV_1 after exercise testing 4 hours after dose administration) was repeated to exclude the 3 youngest children aged 4 or 5 years.

Table 2. Baseline and Demographic Data for the Intention-to-Treat Population

Variable	Value
Age, y	
Mean (SD)	8.8 (2.13)
Range	4–11
Sex, M/F, No. (%)	7/16 (30/70)
Height, mean (SD), cm	137 (13.96)
Body weight, mean (SD), kg	35.9 (11.86)
Time since asthma diagnosis, mean (SD), mo	71 (36.9)
First exercise challenge test at visit 1	
Preexercise	
FEV_1, L	
Mean (SD)	1.75 (0.48)
Range	0.95–3.06
FEV_1, % predicted	
Mean (SD)	86 (13.4)
Range	63–114
Postexercise, % decrease	
Mean (SD)	30 (8.8)
Range	17–50
Second exercise challenge test at visit 1	
Preexercise FEV_1, L	
Mean (SD)	1.71 (0.50)
Range	0.86–2.96
Postexercise, % decrease	
Mean (SD)	29 (9.9)
Range	19–62

Abbreviation: FEV_1, forced expiratory volume in 1 second.

This analysis demonstrated essentially the same treatment effect seen with the full (ITT) study population, with statistical significance for the same treatment comparisons.

Secondary Efficacy Analysis

Values for the maximum percentage decrease in FEV_1 with LOCF at the other time points are given in Table 3, with treatment differences at 15 minutes, 8 hours, and 12 hours depicted in Figure 1. Fifteen minutes after dose administration, formoterol, 12 and 24 μg, was significantly more effective than placebo, as was albuterol ($P < .001$ for all). There were no significant differences between either the 12- or 24-μg dose of formoterol and albuterol ($P = .648$ and $P = .215$, respectively) or between the 2 doses of formoterol ($P = .429$). At 8 hours, both formoterol doses were significantly more effective compared with placebo (12 μg, $P = .002$; 24 μg, $P < .001$), with a smaller but significant difference between albuterol and placebo ($P = .045$). The 8-hour differences between formoterol and albuterol did not reach significance (12 μg, $P = .246$; 24 μg, $P = .058$). By 12 hours, the only remaining significant treatment difference was between formoterol, 24 μg, and placebo ($P = .029$); however, this was not statistically significant in terms of adjustment for multiplicity because the P value exceeded the critical value of .025 according to the Hochberg method.

More albuterol- and placebo-treated patients (n = 10 and 8, respectively) used rescue medication than formoterol-

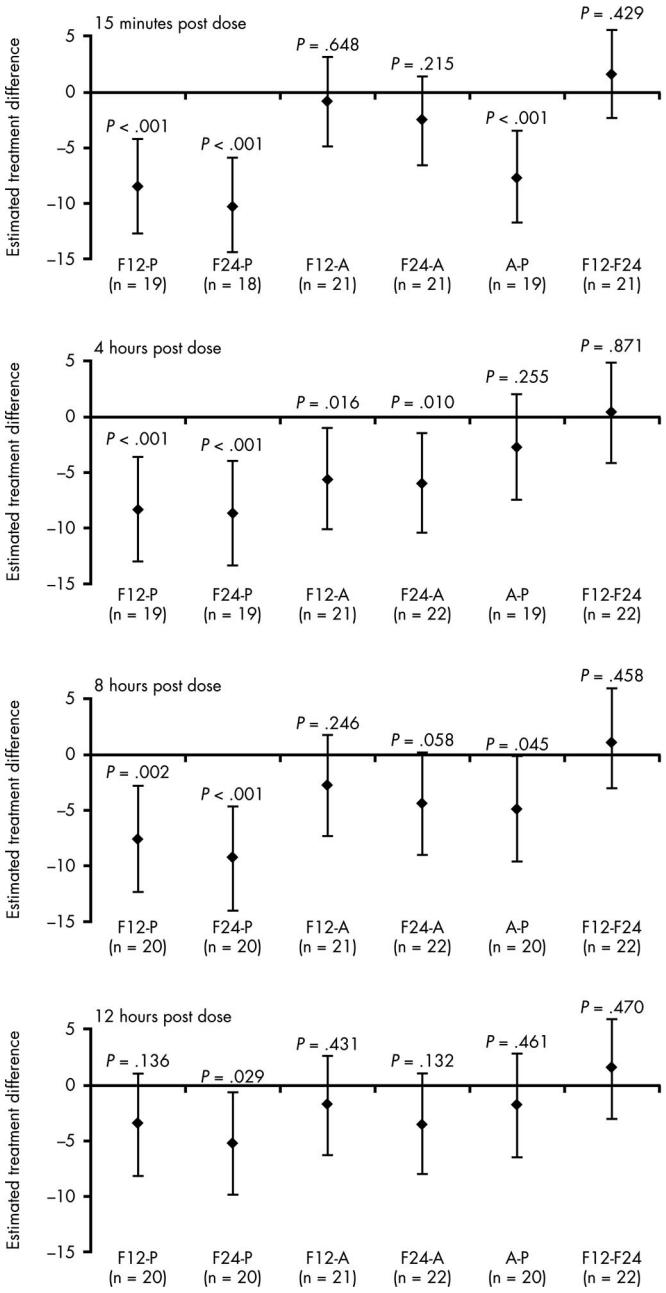

Figure 1. Estimated differences between treatments for maximum percentage decrease in forced expiratory volume in 1 second (FEV_1) from the preexercise value for exercise challenge tests at different postdose times (intention-to-treat population, using last observation carried forward). The treatments compared are shown under each data point. F12 indicates formoterol, 12 μg; F24, formoterol, 24 μg; A, albuterol, 180 μg; and P, placebo. Data points furthest from zero represent the greatest differences between treatments. Mean values for maximum decrease in FEV_1 with each treatment are given in Table 3. Error bars represent 95% confidence intervals.

Table 3. Maximum Percentage Decrease in FEV_1 From Preexercise Values With LOCF by Scheduled Time of Exercise Challenge Testing

Time	Formoterol, 12 μg		Formoterol, 24 μg		Albuterol, 180 μg		Placebo	
	Patients, No.	LSM	Patients, No.	LSM	Patients, No.	LSM	Patients, No.	LSM
15 min	22	2.61	22	1.02	22	3.52	19	11.11
4 h	22	4.96	23	4.60	22	10.54	19	13.26
8 h	22	5.55	23	3.84	22	8.26	20	13.17
12 h	22	7.61	23	5.99	22	9.39	20	11.11

Abbreviations: FEV_1, forced expiratory volume in 1 second; LOCF, last observation carried forward; LSM, least squares mean.

treated patients (12 μg, n = 3; 24 μg, n = 1). Thus, the results of more exercise tests were considered invalid for analysis during albuterol and placebo treatments (10 and 8 tests, respectively) than during formoterol treatment (2 tests with the 12-μg dose and 1 test with the 24-μg dose).

Results for the 8- and 12-hour time points were also analyzed without LOCF, the 15-minute results being unaffected by LOCF. Overall, the 8-hour results were similar apart from larger estimated treatment differences between the formoterol doses and albuterol, which were significant or nearly so (formoterol, 24 μg, $P = .016$; formoterol, 12 μg, $P = .060$). None of the estimated treatment differences at 12 hours were statistically significant.

Using the pretreatment (as opposed to preexercise) value of FEV_1 as a baseline for the maximum percentage decrease in FEV_1 resulted in larger differences between active treatments and placebo. Compared with albuterol and placebo, formoterol (both doses) produced significantly smaller maximum percentage decreases in FEV_1 4, 8, and 12 hours after dose administration (results not shown).

The results were also examined retrospectively to determine the proportions of patients who were protected from EIB (protection being defined as <20% maximum percentage decrease in FEV_1 from the preexercise value) (Fig 2A). Across all time points, formoterol, 12 and 24 μg, afforded protection against EIB for 17 (77%) of 22 and 17 (74%) of 23 patients, respectively, compared with 8 (35%) of 23 patients taking albuterol and 6 (27%) of 22 taking placebo. Using a lower cutoff point defining protection as less than 10% maximum percentage decrease in FEV_1 from the preexercise value, approximately twice the proportion of patients receiving formoterol were protected at all time points (12 μg, 36% [8/22]; 24 μg, 39% [9/23]) compared with albuterol (17% [4/23]) or placebo (18% [4/22]) (Fig 2B).

Safety

Seven of the 23 patients reported an adverse event: 2 during each of the 2 formoterol treatment periods, 3 with albuterol, and 2 with placebo (1 patient reported an event during each of 3 treatment periods). All the events were mild or moderate; none were considered study drug related. The most frequent event was asthma, reported by 2 patients during the formoterol, 24 μg, treatment period; 2 during the albuterol treatment period; and 1 in the placebo period. The other events were aggravated allergy and nausea/vomiting during the formoterol, 12 μg, treatment period; abdominal pain, diarrhea, and vomiting during the albuterol treatment period; and dermatitis during the placebo period. Two patients discontinued trial participation because of adverse events: 1 experienced an asthma exacerbation and the other experienced worsening asthma. Both of these events had onset between visits and were not considered to be causally related to the administration of any trial medication.

There were no differences between treatments in changes in vital signs that were considered to be clinically important. The mean QTc values from before treatment to after treatment showed a 10-millisecond increase and a 5-millisecond decrease with formoterol, 24 and 12 μg, respectively; a 1-millisecond increase with albuterol; and a 1-millisecond decrease with placebo. The increase with formoterol, 24 μg, was modest but statistically significant compared with the other treatments, and individual data were, therefore, scrutinized. No patient experienced QTc prolongation beyond 60 milliseconds. Five patients experienced 30- to 60-millisecond increases (formoterol, 12 μg, n = 1; formoterol, 24 μg, n = 2; albuterol, n = 2; and placebo, n = 2). Four patients experienced a QTc greater than 460 milliseconds: 2 were baseline (predose) measurements, and 1 patient experienced 1 event each during albuterol and placebo treatments. The maximum QTc values after administration of the dose were 449 milliseconds with formoterol, 12 μg; 457 milliseconds with formoterol, 24 μg; 479 milliseconds with albuterol; and 462 milliseconds with placebo.

DISCUSSION

The results of this study involving 23 children aged 4 to 11 years showed that a single dose of formoterol (12 or 24 μg) afforded greater protection against EIB compared with placebo and albuterol. Formoterol gave protection as early as 15 minutes after dose administration and at both doses retained a significant difference over placebo at 4 and 8 hours and at the 24-μg dose at 12 hours. Protection at 15 minutes was not significantly different between formoterol and albuterol, and both doses of formoterol afforded significantly greater protection against EIB 4 hours after dose administration, the predefined primary efficacy variable.

The significant treatment contrasts in favor of both formoterol treatments vs albuterol and placebo were also observed when results were adjusted for multiplicity according to the Hochberg method, and the results were similar whether LOCF was applied or not to the analysis or whether carryover was fitted into the

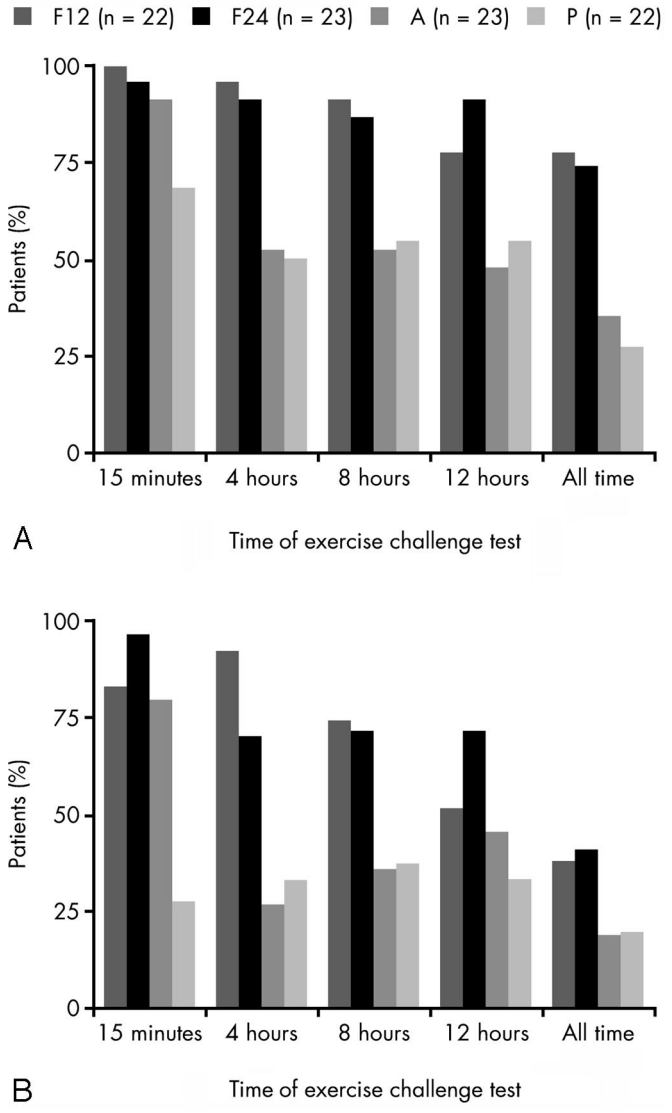

Figure 2. Percentage of patients protected from exercise-induced bronchoconstriction with formoterol, albuterol, and placebo using 2 definitions of protection: patients in whom maximum percentage decrease in forced expiratory volume in 1 second (FEV_1) was less than 20% from preexercise values (A) and less than 10% from preexercise values (without last observation carried forward) (B). F12 indicates formoterol, 12 μg; F24, formoterol, 24 μg; A, albuterol, 180 μg; P, placebo.

ANCOVA model. The consistency of findings between the different methods of analysis confirms the efficacy of formoterol at the 4-hour postdose time point for both doses. The use of rescue medication was more frequent in the albuterol and placebo groups (10 and 8 patients, respectively) compared with the formoterol groups (2 and 1 patient). The analyses at later time points may, therefore, have been biased against formoterol because results in albuterol- and placebo-treated patients could have improved as a result of earlier values being carried forward in the analysis.

Although a treatment difference between formoterol and albuterol was not observed at 12 hours for the maximum percentage decrease in FEV_1, the percentage of patients protected (maximum decrease $<$20%) at 12 hours was higher for both formoterol doses than either albuterol or placebo (Fig 2A). After treatment with formoterol, 12 or 24 μg, 77% and 74% of patients, respectively, were protected across all time points, more than double the percentage protected with albuterol (35%) and placebo (27%). Using a more sensitive cutoff value defining protection as a less than 10% maximum decrease in FEV_1, formoterol again afforded protection for twice the percentage of patients protected with albuterol or placebo (Fig 2B).

Previous studies[5,6] have demonstrated the protective effect of formoterol against EIB in adults with asthma, with onset of protection at 15 minutes and a duration of effect of 12 hours. The results of the present study demonstrate a 15-minute onset of protection and at least an 8-hour duration of effect in children and confirm the results of previous studies[7,8] in pediatric patients showing a protective effect against EIB using formoterol administered from a pressurized MDI.

Exercise-induced bronchoconstriction may have a particularly damaging effect on children's social and physical well-being, preventing their play and sporting activities. A single dose of a long-acting bronchodilator, such as formoterol, may be useful when prevention of EIB is required for most of the day. A simple regimen consisting of a single morning dose may be particularly helpful for schoolchildren, when the parent cannot monitor correct dosing of a shorter-acting agent and school personnel may be unable to take on this responsibility. The low requirement for additional bronchodilator rescue medication observed with formoterol in this study may also be helpful in these respects. In addition, the use of albuterol rescue medication reflects the perception of the child or the observer and may be a more meaningful indicator than, for example, pulmonary function measurements, of what happens in "real-world" practice.

In the present study, treatments were well tolerated and adverse events were few and mild to moderate. Formoterol is approved in the United States for occasional use to prevent EIB and as regular (12 μg twice daily) maintenance treatment for asthma in patients 5 years and older. "Occasional" use for EIB is not defined, and, theoretically, a child who is active on a daily basis might require a daily dose of formoterol. Although such use has not been investigated, studies of regular use of formoterol by children for up to 1 year have reported satisfactory safety and efficacy.[9]

An appropriate approach to managing EIB is first to ensure that the underlying asthma is well controlled with anti-inflammatory therapy tailored to overall asthma severity. This is best managed with an inhaled corticosteroid, but alternatives may include treatment with a leukotriene antagonist or cromones.[3] Albuterol is recommended as single-dose preventive therapy for EIB.[3] Among other agents, orally administered leukotriene antagonists have an onset of effect measured in hours,[15] whereas cromones lack a sufficient duration of effect and would have little advan-

tage over albuterol.[16] Of the 2 long-acting β_2-agonists, formoterol has an onset of effect similar to albuterol and faster than salmeterol.[17] The results of the present and previous studies of formoterol in EIB[5–8] suggest that formoterol is the preferred alternative to albuterol if a longer duration of protective effect is required.

There have been concerns about possible loss of bronchoprotection when β_2-agonist bronchodilators are used regularly.[18] Indeed, a small study[19] in adults suggested that protection against EIB was reduced with regular twice-daily use of formoterol. Similar results have been observed in larger studies[20] in adults with regular use of salmeterol. Although most children whose asthma is well controlled by regular inhaled corticosteroid therapy may be protected against EIB,[2] some children may still exhibit symptoms provoked by exercise.[21] In others, EIB may seem to be an isolated phenomenon, although it is widely acknowledged that in many children, "isolated" EIB may in fact reflect underlying undiagnosed chronic asthma.[22,23] It is suggested that the requirement for daily use of formoterol to prevent EIB should raise a serious question about whether the child is in fact a candidate for maintenance controller therapy with an inhaled corticosteroid or other anti-inflammatory therapy, alone or with added therapy with a long-acting β_2-agonist.

In summary, formoterol was well tolerated and provided effective protection against EIB in the children studied, with early onset and a long duration of effect. The finding that inhalation of a single dose of the powdered form of formoterol (Foradil Aerolizer) can provide prolonged protection against EIB in children is consistent with that of previous studies using formoterol MDIs in protecting against EIB, adding another therapeutic option that may facilitate more normal participation in play and other physical activity for children with asthma.

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Requests for reprints should be addressed to:
Barbara Ziehmer, MD
Novartis Pharmaceuticals Corp
One Health Plaza
East Hanover, NJ 07936-1080
E-mail: barbara.ziehmer@novartis.com

Formoterol, 24 μg bid, and Serious Asthma Exacerbations*

Similar Rates Compared With Formoterol, 12 μg bid, With and Without Extra Doses Taken on Demand, and Placebo

James Wolfe, MD, FCCP; Craig LaForce, MD; Bruce Friedman, MD; William Sokol, MD; Denise Till, MSc; Giovanni Della Cioppa, MD; and Andre van As, MD, PhD, FCCP

Study objectives: **The primary objective was to determine whether high-dose formoterol, 24 μg bid, was associated with more asthma exacerbations compared with lower formoterol doses in patients with stable persistent asthma. Serious asthma exacerbations (life threatening or requiring hospitalization) were the primary end point. Secondary end points included significant exacerbations requiring systemic corticosteroids, all exacerbations, and changes in FEV_1.**

Design: **In a multicenter, placebo-controlled, parallel-group study, patients were randomized to 16 weeks of treatment with formoterol, 24 μg bid; formoterol, 12 μg bid, with up to two additional 12-μg doses daily on demand for worsening symptoms (12 μg bid plus on demand); formoterol, 12 μg bid; or placebo. The formoterol 12-μg-bid plus on-demand regimen was administered open label, while the other three regimens were double blind.**

Setting: **Outpatient clinics.**

Patients: **A total of 2,085 patients aged ≥ 12 years with stable, persistent asthma were enrolled and treated; 65% (n = 1,347) received regular concomitant antiinflammatory therapy during the study.**

Measurements and results: **Nine patients had respiratory-related serious adverse events (SAEs) requiring hospitalization: two patients (0.4%) in the 24-μg-bid group; one patient (0.2%) in the 12-μg-bid plus on-demand group; five patients (0.9%) in the 12-μg-bid group; and one patient (0.2%) in the placebo group. All of these events were asthma related, except for two SAEs in the 12-μg-bid group that were later considered not to be asthma related by independent reviewers who were not associated with the conduct of the study. The proportions of patients with significant asthma exacerbations (requiring systemic corticosteroids) were similar in the 24-μg-bid group (6.3%, 33 of 527 patients), 12-μg-bid group (5.9%, 31 of 527 patients) and placebo group (8.8%, 45 of 514 patients) and lower in the 12-μg-bid plus on-demand group (4.4%, 23 of 517 patients; $p = 0.0057$ vs placebo). All treatments were well tolerated. All formoterol treatment regimens had a significant effect on FEV_1 measured 2 h after dose during the study ($p < 0.0001$ vs placebo); and on predose trough FEV_1 measured at all visits after baseline ($p < 0.002$ vs placebo).**

Conclusions: **Treatment with formoterol, 24 μg bid, was not associated with an increase in serious asthma exacerbations compared with the lower formoterol doses or placebo.**

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Key words: adverse events; Aerolizer; asthma; bronchodilation; exacerbations; formoterol; high dose

Abbreviations: AE = adverse event; CI = confidence interval; DPI = dry powder inhaler; ED = emergency department; FDA = Food and Drug Administration; ICS = inhaled corticosteroids; ITT = intent to treat; LABA = long-acting β_2-agonist; SAE = serious adverse event

The use of inhaled corticosteroids (ICS) is recommended as a rational approach for the management of underlying airway inflammation that results in the many manifestations of asthma. This approach is often supplemented with short-acting, inhaled, β_2-agonist bronchodilators, which provide symptomatic relief. The introduction of long-acting β_2-agonists (LABAs; formoterol and salmeterol) has resulted in improved outcomes when they are used

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concurrently with ICS, compared with use of either monotherapy alone. Both LABAs are classified as controller medications for use in patients with persistent asthma and are usually recommended for use in conjunction with ICS.[1,2]

Formoterol and salmeterol have a similar duration of bronchodilation of at least 12 h, but formoterol has a fast onset of action of < 3 min, whereas salmeterol can take up to approximately 20 min to produce clinically relevant bronchodilation.[3–8] Formoterol has been available for > 10 years, originally as a pressurized metered-dose inhaler and subsequently as a dry powder inhaler (DPI), and has been shown to be well tolerated and effective in long-term studies.[9,10] Formoterol was approved in Europe and worldwide in the mid-1990s; subsequently, a single-dose DPI (Foradil Aerolizer; Novartis Pharmaceuticals; East Hanover, NJ) was approved in 2001 by the US Food and Drug Administration (FDA) for use as maintenance treatment of asthma and COPD at a dose and schedule of 12 μg (one capsule) inhaled bid. Treatment with formoterol DPI has been shown to be effective and well tolerated in children and adults with asthma in studies up to 1 year in duration.[11–15]

*From Allergy and Asthma Associates of Santa Clara Valley Research Center (Dr. Wolfe), San Jose, CA; North Carolina Clinical Research (Dr. LaForce), Raleigh, NC; Allergy, Asthma, Bronchitis and Immunology Associates (Dr. Friedman), Fountain Valley, CA; Health Research Institute (Dr. Sokol), Newport Beach, CA; Novartis Horsham Research Centre (Ms. Till and Dr. Della Cioppa), Horsham, UK; and Novartis Pharmaceuticals (Dr. van As), East Hanover, NJ.

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Dr. van As has a declared conflict of financial interest in that he was an employee of Novartis and owns Novartis shares.
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Correspondence to: James Wolfe, MD, Allergy and Asthma Associates of Santa Clara Valley Research Center, 4050 Moorpark Ave, San Jose, CA 95117; e-mail: aaascv@asthmaresearch.com

The safety of LABAs has been the focus of much recent discussion after a placebo-controlled study in approximately 26,000 patients revealed a small but significant increase in asthma-related deaths among patients receiving salmeterol.[16] In the case of formoterol, concerns were raised about a possible link between the use of higher doses of this agent (24 μg bid via single-dose DPI) and an increase in serious asthma exacerbations, based on findings from two 12-week studies and a 1-year study.[11–13,17] Using the frequency of the serious asthma exacerbations in these three studies, the present study in more than 2000 asthma patients was designed and powered to answer the latter question. We therefore evaluated the safety and efficacy of the 24-μg-bid dose (approved in most countries, but not in the United States) taken for 16 weeks in adolescents and adults with stable persistent asthma compared with the 12-μg-bid regimen (approved in the United States) and an open-label arm that allowed use of formoterol, 12 μg bid, with up to two additional 12-μg doses taken as needed (12 μg bid plus on demand) and placebo. The primary end point was the percentage of patients with serious asthma exacerbations.

Materials and Methods

Study Design

This was a 2,085-patient, multicenter, randomized, parallel-group, double-blind, placebo-controlled study with a 2-week run-in and a 16-week treatment period during which patients visited the clinic at 4-week intervals. At baseline, patients were evaluated for medical history, vital signs, physical examination, history of asthma treatment and asthma exacerbations, bronchodilator reversibility testing, and ECG. Blood and urine samples were collected for laboratory testing. At each visit, vital signs and physical examination were repeated and information was gathered on medication use, adverse events (AEs), and emergency department (ED) visits. FEV_1 was measured at each visit before the administration of study drug or placebo, and 2 h after dose. Patients completed a questionnaire on their satisfaction with their asthma management prior to and at the end of the treatment period.

Inclusion/Exclusion Criteria

Male and female patients aged ≥ 12 years with persistent asthma were enrolled at 194 outpatient asthma clinics across the United States. Among the inclusion criteria were appropriate treatment for asthma according to management guidelines[2]; $FEV_1 \geq 40\%$ of predicted normal following washout from inhaled bronchodilator treatment; and FEV_1 reversibility $\geq 12\%$ after inhalation of up to four puffs of albuterol (360 μg) at screening or documented within the past year.

Exclusion criteria included pregnancy, nursing, or child-bearing potential and absence of reliable contraception; clinically significant cardiovascular disease; malignancy; history of insulin-dependent diabetes mellitus; upper respiratory tract infection 1 month before and during the run-in period; a recent or > 10

pack-year smoking history; ED or hospital treatment for an acute asthma attack 1 month before or during the run-in; and any significant medical condition or laboratory profile that might compromise patient safety or adherence. Also excluded were any patients receiving parenteral, oral, or nebulized β_2-agonists in the 2 weeks before or during the run-in period; systemic corticosteroids, nedocromil, or ketotifen in the 1 month before run-in; astemizole or desensitization therapy initiated in the 3 months before run-in; antihistamines that could affect the QTc interval; nonpotassium-sparing diuretics; β-blockers; quinidine-like agents; and tricyclic antidepressants, fluoxetine, or monoamine oxidase inhibitors. Fixed-combination LABAs and ICS were discontinued, and the same dose of the same ICS was prescribed as monotherapy, with stable treatment for at least 1 month before randomization.

Informed consent was obtained from all patients prior to any study procedures. The study was performed in accordance with the Helsinki Declaration of 1964 (amended 1975, 1983, 1989, 1996) and approved by the review boards of the participating centers.

Study Treatment

Eligible patients were randomized to one of four treatment groups: (1) formoterol, 24 μg bid, double blind; (2) open-label formoterol, 12 μg bid, with up to 2 additional 12-μg daily doses of formoterol as needed for worsening symptoms (12 μg bid plus on demand); (3) formoterol, 12 μg bid, double blind; or (4) placebo, double blind. Study medications were administered by inhalation from a single-dose DPI bid between 6 AM and 9 AM (morning dose) and 6 PM and 9 PM (evening dose). The extra (up to two daily) doses of formoterol in the 12-μg-bid plus on-demand study arm were also administered from the single-dose DPI. The capsules containing formoterol and placebo were identical in appearance. The planned duration of study treatment was 16 weeks.

Concomitant Medication

Patients in the three double-blind treatment groups were allowed rescue medication (albuterol pressurized metered-dose inhaler, 90 μg per actuation; up to eight puffs per day) for worsening symptoms. Patients in the formoterol 12-μg-bid plus on-demand group were allowed up to four puffs per day of albuterol as rescue medication, after receiving the two additional 12-μg daily doses of formoterol on demand. At each postrandomization visit, investigators recorded the number of rescue formoterol capsules inhaled since the last visit. The total formoterol intake was not to exceed 48 μg/d.

Antiinflammatory therapy with inhaled (and intranasal) corticosteroids, leukotriene antagonists, and inhaled cromolyn was recommended but not mandatory. The antiinflammatory regimen was kept stable for at least 3 weeks before randomization. Initiation of recommended antiinflammatory treatment described above was allowed at any time during the course of the study if deemed necessary by the investigator. Sustained-release theophylline was permitted with individual minor dose adjustments as necessary. Systemic corticosteroids or anticholinergic agents were allowed only to treat an intercurrent asthma exacerbation.

Study End Points

Serious Asthma Exacerbations: This was the primary outcome variable of this study, and was the percentage of patients with defined (prior to unblinding the treatment codes) preferred terms in the *Medical Dictionary of Regulatory Activities*, as one or more of the following asthma-related AEs: chest discomfort, asthma, cough, wheezing, dyspnea, dyspnea exacerbated, status asthmaticus, respiratory distress, bronchospasm, acute respiratory failure, and hypoxia. In this context, "serious" signifies that the AE is fatal or life threatening, or requires or prolongs hospitalization.

Significant Asthma Exacerbations: This was defined as asthma-related AEs (using preferred terms as above) that required oral or parenteral corticosteroid use but did not necessarily qualify to be defined as serious.

Combined Serious Asthma Exacerbations, Asthma-Related Discontinuations, and ED Visits for Asthma: In order to increase the chance of detecting any safety signal, this variable combined the proportions of patients experiencing a serious asthma exacerbation or discontinuing the study prematurely due to an asthma-related AE, or having an asthma-related ED visit during the study.

All Asthma-Related AEs: This variable included all asthma-related AEs (regardless of severity).

All AEs newly occurring or worsening in severity during treatment were assessed, and vital signs were monitored. It was planned to follow up all patients in this study for 16 weeks, including those who were discontinued prematurely for any reason.

Efficacy was a secondary objective of the study and was evaluated at clinic visits based on predose and 2-h postdose FEV_1. Patients were asked to avoid taking rescue albuterol for the 8-h period prior to a visit and not to take rescue formoterol after the dose of the previous evening unless absolutely necessary, in order to avoid affecting FEV_1 measurements at that visit. However, any such use of rescue medication was recorded in order to evaluate any differences between groups that could influence the FEV_1 data by rescue treatment intervention.

The questionnaire assessing the patient's satisfaction with their asthma management at the start and end of the treatment period assigned a value from 1 (lowest level) to 5 (highest level of satisfaction) in response to the question, "How do you rate your current asthma treatment and the way it helps you control your asthma?"

Statistical Analysis

The safety and intent-to-treat (ITT) populations comprised all randomized patients who received at least one dose of study medication. Additional subpopulations were defined based on regular use of antiinflammatory medication.

The number of patients having a serious asthma exacerbation, a significant exacerbation, any asthma-related AE, and premature discontinuations due to asthma were compared between treatment groups using Fisher's exact test. The end points involving serious asthma exacerbations and premature discontinuations due to asthma were prospectively determined in the protocol; however, the corresponding inferential analyses were determined *post hoc*. In the original analysis plan, it was decided not to conduct inferential analyses on these end points because of the small number of qualifying events. Likewise, all the subgroup analyses based on antiinflammatory use were determined *post hoc*.

Additionally, the number of patients experiencing a serious asthma exacerbation or a premature discontinuation due to asthma or an ED visit due to asthma (combined end point) was analyzed in the same way. As these three qualifying features are not mutually exclusive, each event with multiple qualifying features was counted only once in the combined end point. This

end point was defined and analyzed *post hoc*. No imputation of events was made for patients discontinuing early for any of these safety variables.

Predose and postdose FEV_1 measurements were analyzed using an analysis of covariance model controlling for treatment, baseline FEV_1, gender, and center. All FEV_1 values were included regardless of rescue medication usage. Vital signs were analyzed using analysis of covariance similar to that used for FEV_1. The patient satisfaction questionnaire was analyzed using the van Elteren test stratified by center. All treatment comparisons were made at the 5% significance level (two sided).

The trial was designed to detect a difference in the percentage of patients having a serious asthma exacerbation between the 24-μg-bid group and the 12-μg-bid group during the 16-week treatment period. Using a two-sided test, approximately 500 patients per group were required to give 80% power to detect a rate of serious asthma exacerbations of 4.5% in the formoterol 24-μg-bid group vs 1.5% in the formoterol 12-μg-bid group as being statistically significant at the 5% level. This trial design, including the assumed rates for serious exacerbations, was prospectively agreed on with the Pulmonary-Allergy Division of the FDA in response to a review of Foradil safety.

Results

Patients

A total of 2,085 patients were treated. Demographic and baseline characteristics of the ITT population were similar across the treatment groups (Table 1), and asthma severity was comparable. Most patients demonstrated a stable history of asthma in the previous year: 20.4% (426 of 2,085 patients) had nonscheduled physician visits, 16.7% (349 of 2,085 patients) had exacerbations that were treated by oral corticosteroids, and 6.7% (140 of 2,085 patients) had ED visits for asthma. Hospitalizations were rare in the year before enrollment (1.5%; 32 of 2,085 patients).

The numbers of patients in the ITT population and analysis subpopulations based on the use of regular antiinflammatory therapy are given in Table 2. Nearly two thirds of the patients (62.4%, 1,302 of 2,085 patients) received regular antiinflammatory therapy, typically ICS, throughout the study. Forty-five patients (2.2%) commenced regular antiinflammatory treatment during the study. The majority of patients (88.2%, 1,838 of 2,085 patients) received study treatment for at least 3 months (> 84 days), and most (62.7%, 1,307 of 2,085 patients) received it for at least 4 months (> 112 days).

Overall, 14.1% (294 of 2,085 patients) discontinued treatment. Discontinuation rates were similar in each of the treatment groups: 14.0% (74 of 527 patients) in the formoterol 24-μg-bid group, 13.2% (68 of 517 patients) in the formoterol 12-μg-bid plus

Table 1—*Baseline Demographics and Disease Characteristics (ITT Population)*

Variables	Formoterol, 24 μg bid (n = 527)	Formoterol, 12 μg bid Plus on Demand (n = 517)	Formoterol, 12 μg bid (n = 527)	Placebo (n = 514)
Age, yr				
Mean (SD)	38.5 (15.96)	36.9 (15.93)	39.2 (17.24)	37.8 (15.76)
Median	38.0	37.0	39.0	38.0
Range	12–78	12–76	12–82	12–81
Age group, No. (%)				
12–18 yr	72 (13.7)	85 (16.4)	81 (15.4)	76 (14.8)
19–64 yr	426 (80.8)	410 (79.3)	403 (76.5)	410 (79.8)
65–74 yr	26 (4.9)	20 (3.9)	32 (6.1)	25 (4.9)
> 74 yr	3 (0.6)	2 (0.4)	11 (2.1)	3 (0.6)
Male gender, No. (%)	234 (44.4)	240 (46.4)	251 (47.6)	211 (41.1)
Race, No. (%)				
White	411 (78.0)	401 (77.6)	430 (81.6)	402 (78.2)
Black	75 (14.2)	73 (14.1)	59 (11.2)	61 (11.9)
Oriental	11 (2.1)	11 (2.1)	10 (1.9)	14 (2.7)
Other	30 (5.7)	32 (6.2)	28 (5.3)	37 (7.2)
Duration of asthma, yr				
Mean (SD)	21.1 (14.09)	19.8 (14.11)	21.1 (14.52)	20.1 (14.08)
Median	18.0	16.0	18.0	17.0
Range	0–72	0–66	0–80	0–71
FEV_1 at baseline, L				
Mean (SD)	2.35 (0.71)	2.42 (0.69)	2.35 (0.70)	2.37 (0.70)
Range	0.82–4.95	0.93–4.78	0.75–5.01	0.67–4.53
FEV_1 at baseline, % predicted				
Mean (SD)	68.5 (14.85)	69.5 (13.78)	68.2 (13.20)	69.0 (13.24)
Range	35.2–123.6	36.6–119.7	38.7–105.5	39.9–107.8
FEV_1 reversibility at screening, %				
Mean (SD)	23.1 (16.69)	21.4 (12.33)	23.2 (14.88)	22.6 (13.01)
Range	− 15.4–196.4	− 4.4–121.9	− 8.1–121.8	− 7.4–119.2

Table 2—*Use of Antiinflammatory Therapy During Study

Groups	Formoterol, 24 μg bid	Formoterol, 12 μg bid Plus on Demand	Formoterol, 12 μg bid	Placebo
Treated patients (ITT and safety populations)	527 (100)	517 (100)	527 (100)	514 (100)
Patients receiving no regular antiinflammatory therapy during study	182 (34.5)	186 (36.0)	196 (37.2)	174 (33.9)
Patients receiving regular antiinflammatory therapy throughout study	338 (64.1)	318 (61.5)	322 (61.1)	324 (63.0)
Patients receiving regular antiinflammatory therapy added after baseline	7 (1.3)	13 (2.5)	9 (1.7)	16 (3.1)

*Data are presented as No. (%).

on-demand group, 13.7% (72 of 527 patients) in the formoterol 12-μg-bid group, and 15.6% (80 of 514 patients) in the placebo group. The most common primary reasons for discontinuation were AEs (4.9% overall: 7.4% [39 of 527 patients] for formoterol 24 μg bid [the increase in this group was mainly due to β_2-adrenoceptor-mediated effects such as tremor; see later section for details]; 4.1% [21 of 517 patients] for formoterol 12 μg bid plus on demand; 4.2% [22 of 527 patients] for formoterol 12 μg bid, and 4.1% [21 of 514 patients] for placebo) and withdrawal of consent (3.7% overall: 3.0% [16 of 527 patients] for formoterol 24 μg bid; 3.7% [19 of 517 patients] for formoterol 12 μg bid plus on demand; 2.5% [13 of 527 patients] for formoterol 12 μg, and 5.6% [29 of 514 patients] for placebo). Other reasons for dropout were loss of patient to follow-up (1.8% overall), protocol violation (1.7%), unsatisfactory therapeutic effect (1.0%), administrative problems (0.8%), and abnormal (nonblood) test procedure results (0.2%).

Safety Results

Serious Asthma Exacerbations: Nine patients (< 1% in each treatment group) had serious respiratory-related adverse events, all needing hospitalization (Table 3). Figure 1 shows the estimated differences between groups in the percentage of patients with these events. There were no statistically significant differences between the treatment groups ($p > 0.21$).

Table 3—*Respiratory-Related SAEs (Requiring Hospitalization)*

Treatments	No.	No.	%	95% CI
Formoterol, 24 μg bid	527	2	0.4	0–0.9
Formoterol, 12 μg bid plus on demand	517	1	0.2	0–0.6
Formoterol, 12 μg bid	527	5*	0.9	0.1–1.8
Placebo	514	1	0.2	0–0.6
Formoterol combined (three groups)	1,571	8	0.5	0.2–0.9

*Two patients had respiratory events that were not asthma related.

An assessment of the medical histories of the nine events revealed that two events, both in the lower-dose formoterol 12-μg-bid group, were unrelated to asthma. An independent assessment of the serious asthma events in this trial was recorded in a report at the time of the FDA Pulmonary and Allergy Diseases Advisory Committee meeting of July 13, 2005 on the safety of β_2-agonists.[18] The two cases deemed not to be asthma related were as follows: (1) a 78-year-old, white woman who had a myocardial infarction on day 43 of the study and had severe breathlessness as a result, and (2) a 37-year-old white woman who had severe gastroesophageal reflux and was hospitalized for pneumonia on day 63 of the study. When these two events are excluded from the analysis, the incidence of patients experiencing a serious exacerbation in the formoterol 12-μg-bid group is 0.6% (95% confidence interval [CI], 0.0 to 1.2%). The distribution of these events showed no dose-response relationship. There were no statistically significant differences between any groups ($p > 0.62$).

Significant Asthma Exacerbations Requiring Systemic Corticosteroids: The percentage of patients with significant asthma exacerbations, *ie*, requiring a course of oral or parenteral corticosteroid, were 6.3% (33 of 527 patients) in the formoterol 24-μg-bid group, 4.4% (23 of 517 patients) in the formoterol 12-μg-bid plus on-demand treatment group, 5.9% (31 of 527 patients) in the formoterol 12-μg-bid group, and 8.8% (45 of 514 patients) in the placebo group (Table 4). The only statistically significant treatment contrast occurred between the formoterol 12-μg-bid plus on-demand group and placebo group ($p = 0.0057$). Among patients receiving regular antiinflammatory therapy (Table 4), the formoterol treatment groups had fewer patients with significant exacerbations (5 to 7%) compared with placebo (11%); this difference was statistically significant for the formoterol 12-μg-bid plus on-demand group compared with placebo ($p = 0.0059$). In patients without regular antiinflammatory therapy (Ta-

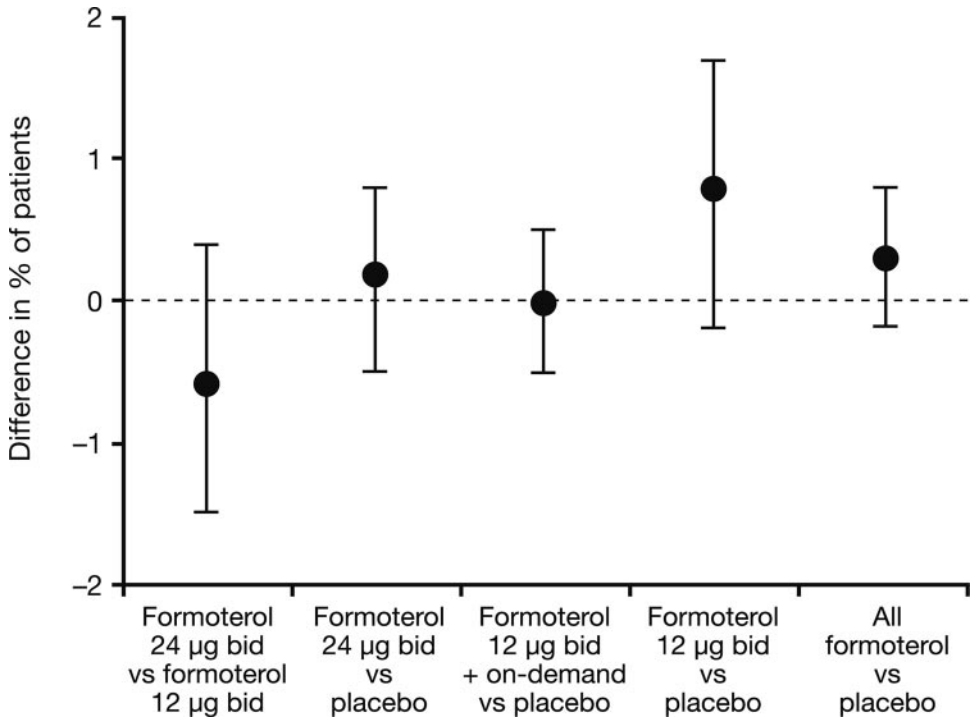

FIGURE 1. Estimated treatment differences (with 95% CIs) for percentage of patients with a respiratory-related SAE.

ble 4), proportions of patients with significant exacerbations were similar in all the treatment groups ($p > 0.46$).

Combined Serious Asthma Exacerbations, Asthma-Related Discontinuations, and ED Visits for Asthma: The proportions of patients experiencing a serious asthma exacerbation or discontinuing the study prematurely due to an asthma-related AE, or having an asthma-related ED visit during the study on the four treatments were as follows in the following subgroups: (1) all patients: 4.2% (22 of 527 patients) in the 24-µg-bid group, 3.5% (18 of 517 patients) in the formoterol 12-µg-bid plus on-demand group, 3.0% (16 of 527 patients) in the 12-µg-bid group, and 4.5% (23 of 514 patients) in the placebo group. There were no statistically significant differences between the treatments ($p > 0.25$); (2) patients who received regular antiinflammatory therapy: 4.1% (14 of 345 patients) in the 24-µg-bid group, 2.4% (8 of 331 patients) in the formoterol 12-µg-bid plus on-demand group, 2.4% (8 of 331 patients) in the 12-µg-bid group, and 4.1% (14 of 340 patients) in the placebo group ($p > 0.27$ for all pairwise comparisons); (3) patients who did not receive regular antiinflammatory therapy: 4.4% (8 of 182 patients) in the 24-µg-bid group, 5.4% (10 of 186 patients) in the formoterol 12-µg-bid plus on-demand group, 4.1% (8 of 196 patients) in the 12-µg-bid group, and 5.2% (9 of 174 patients) in the

Table 4—*Patients With Significant Asthma Exacerbations Requiring Systemic Corticosteroids**

Variables	Formoterol, 24 µg bid	Formoterol, 12 µg bid Plus on Demand	Formoterol, 12 µg bid	Placebo
All patients (safety population)	33/527 (6.3)	23/517 (4.4)†	31/527 (5.9)	45/514 (8.8)
Patients receiving antiinflammatory therapy (throughout study or added after baseline)	23/345 (6.7)	16/331 (4.8)‡	23/331 (6.9)	36/340 (10.6)
Patients without regular antiinflammatory therapy during study	10/182 (5.5)	7/186 (3.8)	8/196 (4.1)	9/174 (5.2)

*Data are presented as No./total (%).

†Treatment difference vs placebo was significantly different ($p = 0.0057$).

‡Treatment difference vs placebo was significantly different ($p = 0.0059$).

placebo group ($p > 0.62$ for all pairwise comparisons).

All Asthma-Related AEs: The proportion of patients with any asthma-related AEs was similar in the formoterol 24-μg-bid and 12-μg-bid groups and not significantly different from placebo ($p > 0.38$). Significantly fewer patients had asthma-related AEs in the formoterol 12-μg-bid plus on-demand group than in the placebo group ($p = 0.0094$) [Table 5].

When the total number of asthma-related AEs was broken down into those patients with and without antiinflammatory treatment, similar results were noted (Table 5). In the former, fewer patients in the formoterol 24-μg-bid and 12-μg-bid groups had asthma-related AEs compared with placebo, although these differences were not significantly different ($p > 0.29$). There was, however, a significant difference between the formoterol 12-μg-bid plus on-demand group and placebo ($p = 0.0092$). In patients not receiving antiinflammatory medication, the differences between groups were smaller, again with no statistical significance ($p > 0.51$).

The proportions of patients with asthma-related AEs leading to premature discontinuation were not statistically significantly different between any groups ($p > 0.25$) [Table 5]. When examining the asthma-related discontinuations in patients receiving antiinflammatory treatment, there were no significant differences between any groups ($p > 0.14$). Similar data, but with smaller differences, were obtained for patients not receiving antiinflammatory treatment ($p > 0.42$) [Table 5].

Other AEs

Overall AE rates are shown in Table 6. Most were mild or moderate in severity. Overall, 9% of patients had AEs that were suspected as being related to study drug: 15% in the 24-μg-bid treatment group, and 6%, 8%, and 6% for formoterol 12-μg-bid plus on-demand group, formoterol 12-μg-bid group, and placebo, respectively. The higher rate in the 24-μg-bid group was primarily related to higher rates of tremor, "feeling jittery," and insomnia, which are typical for the β_2-agonist class.[19] These were also the primary cause for the increased dropout rate among those patients who discontinued treatment because of an AE in the 24-μg-bid group (overall rate, 7.0% [37 of 527 patients], compared with 3.9% [20 of 517 patients] in the 12-μg-bid plus on-demand group, 3.8% [20 of 527 patients] in the 12-μg-bid group, and 4.1% [21 of 514 patients] in the placebo group). In the formoterol 24-μg-bid group, no case of tremor and only one report of insomnia were classified as severe.

The number of patients with cardiac disorders was low and comparable across treatment groups (seven patients in the 24-μg-bid group, five patients in the 12-μg-bid plus on-demand group, six patients in the 12-μg-bid group, and four patients in the placebo group). All cases were mild or moderate in severity, apart from two patients in the 12-μg-bid group: one patient with frequent ventricular extrasystoles and another patient who had a myocardial infarction.

The frequency of serious AEs (SAEs) was low and similar across the treatment groups (1 to 2%). Two patients had SAEs that were suspected to be related to study medication. One patient in the 12-μg-bid group (the same patient mentioned previously) had a myocardial infarction and respiratory distress. One patient in the placebo group required hospitalization for an asthma exacerbation. In both cases, study medication was discontinued. There were no deaths during the study.

Vital Signs

There were no clinically meaningful differences between treatment groups in pulse rate and BP.

Patient Satisfaction Questionnaire

The scores showed that more patients in the active treatment groups believed their asthma control was

Table 5—*Patients With Asthma-Related AEs and Withdrawals Due to Asthma-Related AEs**

Variables	Formoterol, 24 μg bid	Formoterol, 12 μg bid Plus on Demand	Formoterol, 12 μg bid	Placebo
Any asthma-related AEs	72/527 (13.7)	53/517 (10.3)†	74/527 (14.0)	81/514 (15.8)
Patients receiving antiinflammatory therapy	48/345 (13.9)	33/331 (10.0)‡	49/331 (14.8)	58/340 (17.1)
Patients not receiving antiinflammatory therapy	24/182 (13.2)	20/186 (10.8)	25/196 (12.8)	23/174 (13.2)
Withdrawals due to asthma-related AEs	12/527 (2.3)	7/517 (1.4)	7/527 (1.3)	12/514 (2.3)
Patients receiving antiinflammatory therapy	9/345 (2.6)	3/331 (0.9)	5/331 (1.5)	8/340 (2.4)
Patients not receiving antiinflammatory therapy	3/182 (1.6)	4/186 (2.2)	2/196 (1.0)	4/174 (2.3)

*Data are presented as No./total (%).

†Treatment difference vs placebo is significantly different ($p = 0.0094$).

‡Treatment difference vs placebo is significantly different ($p = 0.0092$).

Table 6—*Patients With Most Frequent AEs (≥ 2% for Any Group) [Safety Population]

Variables	Formoterol, 24 μg bid (n = 527)	Formoterol, 12 μg bid Plus on Demand (n = 517)	Formoterol, 12 μg bid (n = 527)	Placebo (n = 514)
Patients with AEs	321 (60.9)	285 (55.1)	279 (52.9)	291 (56.6)
AEs, No.	674	530	630	552
AEs, preferred term				
Asthma	56 (10.6)	39 (7.5)	53 (10.1)	68 (13.2)
Upper respiratory tract infection	49 (9.3)	59 (11.4)	49 (9.3)	63 (12.3)
Sinusitis	25 (4.7)	24 (4.6)	32 (6.1)	22 (4.3)
Nasopharyngitis	32 (6.1)	39 (7.5)	28 (5.3)	25 (4.9)
Headache	18 (3.4)	20 (3.9)	23 (4.4)	23 (4.5)
Pharyngolaryngeal pain	15 (2.8)	10 (1.9)	17 (3.2)	11 (2.1)
Nasal congestion	9 (1.7)	13 (2.5)	17 (3.2)	5 (1.0)
Bronchitis	11 (2.1)	9 (1.7)	16 (3.0)	8 (1.6)
Cough	10 (1.9)	13 (2.5)	15 (2.8)	7 (1.4)
Tremor	25 (4.7)	6 (1.2)	5 (0.9)	3 (0.6)
Viral upper respiratory tract infection	12 (2.3)	3 (0.6)	5 (0.9)	6 (1.2)
Feeling jittery	16 (3.0)	3 (0.6)	2 (0.4)	2 (0.4)
Insomnia	14 (2.7)	3 (0.6)	2 (0.4)	4 (0.8)

*Data are presented as No. (%) unless otherwise indicated.

improved during the study compared with placebo. At baseline, the number of patients recording scores of 4 or 5 (the two highest levels of satisfaction) was 57% (24 μg bid), 56% (12 μg bid plus on demand), 60% (12 μg bid), and 53% (placebo). At the final visit, this had increased to 73 to 76% for the formoterol groups and had remained similar for the placebo group (54%). Results were statistically significantly in favor of formoterol (all three groups; $p < 0.0001$) compared with placebo. The formoterol 12-μg-bid plus on-demand group (76%) and formoterol 12-μg-bid group (73%) were significantly different ($p < 0.01$).

Efficacy

All three formoterol treatment groups achieved statistically significant ($p < 0.0001$) and clinically relevant estimated treatment differences of 270 to 320 mL compared with placebo in FEV_1 measured 2 h after dose after the first dose and after 16 weeks of treatment (Fig 2). A significant treatment difference of ≥ 240 mL between formoterol treatment regimens and placebo was maintained at all study visits ($p < 0.0001$). Comparisons between the formoterol treatment groups (not shown in Fig 2) showed that there was a 50-mL statistically significant difference between the formoterol 24-μg-bid and 12-μg-bid groups ($p = 0.0065$) in favor of the higher dose for FEV_1 measured after the first dose, but not at the end of 16 weeks of treatment.

Predose FEV_1 was consistently statistically significantly superior in the three formoterol treatment groups compared with placebo at weeks 4, 8, 12, and 16 ($p \leq 0.0012$), with a consistent estimated treatment difference of approximately 100 mL. There were no clinically relevant or statistically significant differences between the three formoterol groups at any time point.

During the 8-h period prior to the study visit at week 16 (when patients were asked to refrain from using rescue medication), rescue albuterol was used by 12.0% (55 of 458 patients) in the formoterol 24-μg-bid group, 9.7% (44 of 453 patients) in the formoterol 12-μg-bid plus on-demand group, 10.1% (46 of 457 patients) in the 12-μg-bid group, and 15.5% (68 of 438 patients) in the placebo group, which represents a decline in all groups of one to two percentage points from week 4. In the formoterol 12-μg-bid plus on-demand group, 62% (289 of 446 patients) used rescue formoterol at least once during the first 4 weeks of treatment, declining to 48.6% (209 of 430 patients) in the final 4 weeks.

Discussion

This study was carried out as a postapproval safety commitment to the FDA. The concern that prompted the study is summarized in an article by Mann and colleagues[17] published in 2003. Mann and colleagues[17] reviewed the three pivotal trials submitted to the FDA to support the approval of Foradil Aerolizer (Novartis Pharmaceuticals) in the United States, published individually elsewhere.[11–13] Each of these trials showed a somewhat higher incidence of asthma-related SAEs in patients treated with formoterol 24 μg bid compared with those receiving formoterol 12 μg bid and placebo. Only one of the studies[12] also showed a small imbalance for the formoterol 12-μg-bid dose vs placebo. Mann and colleagues[17] concluded that regular treatment with

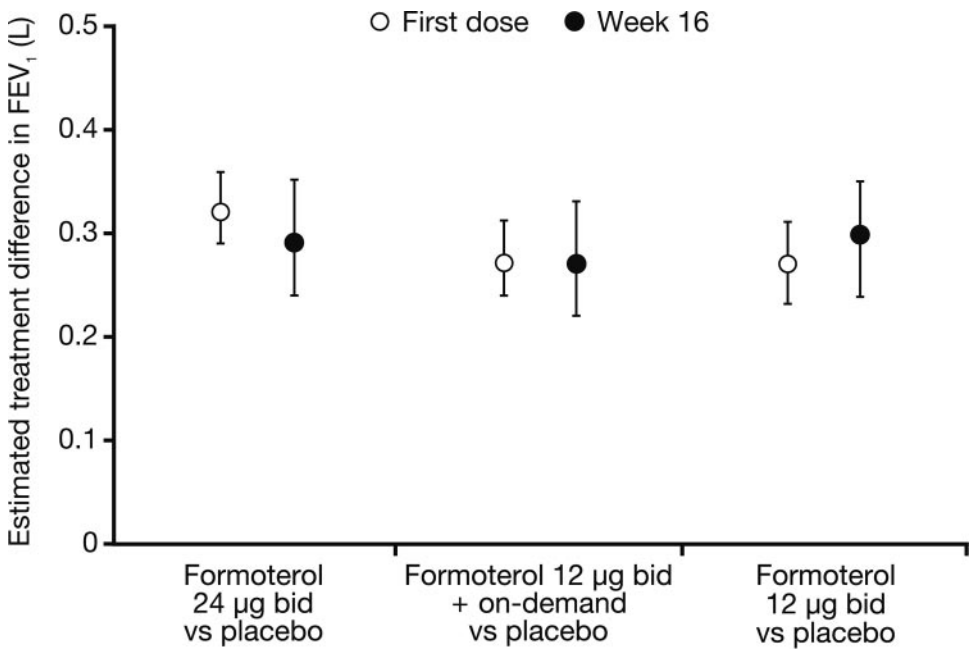

FIGURE 2. Estimated treatment differences (with 95% CIs) for FEV_1 measured 2 h after dose after first dose (open circles) and after 16 weeks of treatment (closed circles) for formoterol treatments vs placebo. All estimated treatment differences were statistically significant ($p < 0.0001$).

high-dose formoterol (24 μg bid) may be associated with more frequent serious asthma exacerbations compared with the lower dose of 12 μg that was approved in the United States. The primary objective of the present study was to test the hypothesis of a dose-related increase in serious asthma exacerbations. Data from other large studies conducted with formoterol Aerolizer did not reflect a higher incidence of asthma-related SAEs in patients treated with formoterol 24 μg bid compared with those receiving formoterol 12 μg bid and placebo.[20]

Another large safety study that raised a related concern, although more specific to mortality, is the Salmeterol Multicenter Asthma Research Trial (SMART), in which the long-acting β_2-agonist salmeterol was compared to placebo. This study, involving > 26,000 patients, was prematurely halted after interim findings suggested patients treated with salmeterol were at higher risk of asthma-related deaths and "near-death" experiences (intubation and mechanical ventilation) compared with those receiving placebo. The SMART study is published in this issue.[16]

No deaths occurred in the present study. There were very few serious asthma-related exacerbations, far fewer than expected in the planning of the sample size based on previous data. Additionally, the results do not confirm the previous observation of a dose-dependent increase in serious asthma exacerbations. The primary end point of the study, serious asthma exacerbations, was no different from placebo in all three formoterol treatment arms, and the overall incidence was < 1%.

An accepted and clinically meaningful category of asthma exacerbations is represented by those patients requiring a course of systemic corticosteroids (referred to as a *significant asthma exacerbation* in the present study). There were fewer significant asthma exacerbations in the formoterol groups than in the placebo group, although statistical significance was only reached in the contrast between the open-label formoterol 12-μg-bid plus on-demand group and placebo (Table 4).

By combining serious asthma exacerbations and/or premature discontinuations due to asthma and/or ED visits due to asthma as a *post-hoc* analysis, a larger number of events becomes available for analysis and makes the chance of detecting a safety signal more meaningful. This analysis showed a very similar rate across the three formoterol dose levels and placebo. While this study was not designed to compare patients receiving antiinflammatory medications or not, for the combined end point we observed a slightly higher frequency of events in patients not receiving concomitant antiinflammatory medications than in those receiving them. Therefore, in keeping with currently accepted guidelines, it is recommended that LABAs be used in conjunction with an appropriate antiinflammatory agent.

The present study was designed with safety as the

primary outcome, while efficacy (FEV_1) was a secondary outcome. As expected, relative to placebo, each of the three formoterol treatment regimens had a significant effect on lung function measured before the morning dose of study treatment and measured 2 h after dose. The measurements of patient satisfaction with their asthma management favored the active treatment groups and were consistent with the improvements in FEV_1, indicating that formoterol use was associated with improved asthma control. This improved control is also reflected in the lower frequency of asthma-related events in the formoterol treatment groups compared with placebo (Tables 4, 5). This difference reached statistical significance in the open-label formoterol 12-μg-bid plus on-demand group as compared with placebo. This suggests that, with the exception of serious asthma exacerbations, the less serious events can be better controlled with the on-demand use of formoterol together with regular use than with albuterol on demand. This was the only open-label treatment arm of the study, and these results should be interpreted with caution.

Although the frequency of serious asthma AEs was smaller than anticipated, this study does not suggest an increased rate of clinically serious exacerbations in formoterol-treated patients, either dose related or overall. This conclusion is further supported by the fact that there was no difference in the frequency of significant asthma exacerbations requiring oral steroids or an increase in frequency of all asthma-related events combined compared with placebo.

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Appendix

The principal investigators and site locations were as follows: Dr. Francisco Candal, Northshore Research, Slidell, LA; Dr. Stephen Kreitzer, Tampa Medical Research Associates, Tampa, FL; Dr. Sherwin Gillman, Division of Allergy, Asthma & Immunology, Orange, CA; Dr. Catherine Van Kerckhove, Catherine Kolehmainen, Littleton, CO; Dr. Lawrence J. Sindel, Pulmonary Associates, P.C., Mobile, AL; Dr. Ken Cohen, New West Physicians Clinical Research, Golden, CO; Dr. Robert Nathan, Asthma and Allergy Associates, PC, Colorado Springs, CO; Dr. Kenneth Kim, West Coast Clinical Trials, Long Beach, CA; Dr. Paul Qaqundah, Pediatric Care Medical Group, Huntington Beach, CA; Dr. Stephen Tilles, A.S.T.H.M.A., Inc., Seattle, WA; Dr. Anthony DeMeo, Diablo Clinical Research, Inc., Walnut Creek, CA; Dr. Tonny Tanus, Lotus Medical Center of Allergy Asthma, Bakersfield, CA; Dr. Jacob Pinnas, Arizona Clinical Studies, Tucson, AZ; Dr. Amy Silverthorn, Arizona Pulmonary Specialists, Phoenix, AZ; Dr. Robert Kearl, Arizona Pulmonary Specialists, Phoenix, AZ; Dr. Henry Gong, USC Rancho Los Amigos Medical Center, Downey, CA; Dr. Cash Beechler, Arizona Pulmonary Specialists, LTD, Scottsdale, AZ; Dr. Leonard Caputo, The Asthma and Allergy Institute, Mobile, AL; Dr. Andrew Davidson, Allergy & Asthma Consultants, LLP, Charleston, SC; Dr. Marc Gottlieb, Diagnostic and Medical Clinic, PA, Mobile, AL; Dr. Pragnesh Patel, Allergy and Asthma Specialists, Altamonte Springs, FL; Dr. Andrew Martin, Asthma & Allergy Clinical Research Center, New Brunswick, NJ; Dr. Bernard Levine, Pulmonary Associates, PA, Phoenix, AZ; Dr. Michael Manning, Allergy and Immunology Association, Scottsdale, AZ; Dr. Nancy Ostrom, Asthma & Allergy Medical Group & Research Center, San Diego, CA; Dr. Sammy Campbell, VA Hospital, Pulmonary/1–111A, Tucson, AZ; Dr. Maurice Archuleta, Rocky Mountain Clinical Research, Golden, CO; Dr. Linda Ford; The Asthma and Allergy Center, PC, Papillion, NE; Dr. Thomas Kaelin, Low Country Lung and Critical Care, PA, Charleston, SC; Dr. Albert Finn, Radiant Research, Charleston-North Charleston, SC; Dr. Graham Scott, Charleston Pulmonary Associates, Charleston, SC; Dr. J. Allen Meadows; Drud Research and Analysis Corporation, Montgomery, AL; Dr. Jim Christensen, Nevada Access to Research & Education Society, Las Vegas, NV; Dr. Andrew Grant, UTMB, Galveston, TX; Dr. Warren Pleskow, Radiant Research, San Diego North, Encinitas, CA; Dr. John Lafata, Progressive Clinical Research, Vista, CA; Dr. David Laman, Consolidated Clinical Trials, Inc., Pittsburgh, PA; Dr. William Calhoun, UPMC, Pittsburgh, PA; Dr. Karl Sitz, Little Rock Allergy & Asthma Clinic, PA, Little Rock, AR; Dr. Manuel Lopez, Tulane University Health Sciences Center, New Orleans, LA; Dr. Maria Franco, Miami Children's Hospital, Miami, FL; Dr. F. Charles Hiller, University of Arkansas for Medical Sciences, Little Rock, AR; Dr. Louis Kalish, Rx Research, Woodstock, GA; Dr. Dean Atkinson, Oklahoma Allergy & Asthma Clinic, Oklahoma City, OK; Dr. Kevin Kelly, Medical College of Wisconsin Asthma & Allergy Center, Milwaukee, WI; Dr. Edward Lisberg, Asthma & Allergy Center of Chicago, River Forest, IL; Dr. Mercedes Samson; B.P. Center Clinical Trials, Inc., Buena Park, CA; Dr. M. Ross Thomas, Midwest Allergy & Asthma Clinic Omaha, NE, Dr. James Baker; Allergy Associates Medical Center, Portland, OR; Dr. Keith Klatt, Radiant Research, Portland, OR; Dr. Richard Gower, Rockwood Clinic, PS, Spokane, WA; Dr. Paul Scheinberg, Atlanta Pulmonary Group, Atlanta, GA; Dr. David Graft, Park Nicollet Institute, Asthma & Allergy Research Center, Minneapolis, MN; Dr. James Cury, Shands Jacksonville Medical Center, Jacksonville, FL; Dr. Alan Aven, Arlington Heights, IL; Dr. Michael Rowe, Michigan Asthma & Allergy Center, Novi, MI; Dr. Peter Schochet, Presbyterian Hospital of Plano, Plano, TX; Dr. Jeffrey Leflein, Respiratory Medicine Research Institute, Ypsilanti, MI; Dr. Gregory Gottschlich, New Horizons Clinical Research, Cincinnati, OH; Dr. Jeff Craig, Sterling Research Group, LTD, Cincinnati, OH; Dr. Phillip Korenblat, The Clinical Research Center, LLc, St. Louis, MO; Dr. J. Allen Cooper, Birmingham VA Medical Center, Birmingham, AL; Dr. Robert Settipine, Allergy and Asthma Center, Providence, RI; Dr. Scott Yates, North Texas Medical Research, The Colony, TX; Dr. Brian Carlin, Consolidated Clinical Trials, Inc., Pittsburgh, PA; Dr. John Yarbrough, Allergy & Asthma Clinic of Northeast Georgia, Gainesville, GA; Dr. Robin Levy, Family Allergy and Asthma Center, Atlanta, GA; Dr. Randy S. Stoloff, Empire State Asthma & Allergy Treatment & Research Center, Plattsburgh, NY; Dr. Arthur DeGraff, Physician's Research Center, Inc., Hartford, CT; Dr. Hugh Windom, Asthma & Allergy Research Center, Sarasota, FL; Dr. Carolyn Comer, Alabama Allergy & Asthma Center, Birmingham, AL; Dr. Jonathan Bernstein, Berstein Clinical Research Center, Cincinnati, OH; Dr. Paul Chervinsky, New England Research Center, North Dartmouth, MA; Dr. Suzanne Weakley, Clinical Trials, North Houston, Houston, TX; Dr. Lyndon Mansfield, El Paso Institute for Medical R&D, El Paso, TX; Dr. Jacques Caldwell, Radiant Research, Daytona Beach, FL; Dr.

Michael Lawrence, Center for Clinical Research, Taunton, MA; Dr. Juan Sotomayer, Allergy and Asthma Diagnostic Office, Liverpool, NY; Dr. John J. Condemi, Allergy, Asthma & Immunology of Rochester Research Center, Rochester, NY; Dr. Howard Knapp, Deaconess Research Division, Billings, MT; Dr. David Valacer, New York Presbyterian-Cornell Weil, New York, NY; Dr. Janet Despot, Cardinal Respiratory, PC, Springfield, IL; Dr. Harmon Davis, IMG Clinical Research Center, LLC, Cheyenne, WY; Dr. A.M. Aminian, Allergy Institute Fresno, CA; Dr. Christopher Smith, Asthma and Allergy Associates, Ithaca, NY; Dr. Wilfred Beaucher, Certified Research Consultants, Chelmsford, MA; Dr. Azmi Farag, Mountain View Clinical Research, Denver, CO; Dr. Judith Kirstein, Jordan Valley Family Clinic, West Jordan, UT; Dr. Pardeep Rihal, Christus St. Catherines, Katy, TX; Dr. Thomas Ellis, Medical Specialty Clinic, Jackson, TN; Dr. Anthony Rooklin, Allergy Research Associates, Upland, PA; Dr. Alexander Shepherd, University of Texas Health Science Center at San Antonio, San Antonio, TX; Dr. Kim Jones, Louisianna State University Health Sciences Center, Shreveport, LA; Dr. Narinder Arora, Charlottsville Medical Research, Charlottsville, VA; Dr. Leslie Couch, University of Texas Health Center at Tyler, Tyler, TX; Dr. Jeffrey Wald, Kansas City Allergy and Asthma Associates, Overland Park, KS; Dr. Curtis Mello, JM Clinical Trials, Inc., Swansea, MA; Dr. Bruce Pfuetze, Multi-Specialty Clinical Research, College Park Family Care Center, Overland Park, KS; Dr. Matthew Beacom, Dr. Thomas A. McKnight, Fremont, NE; Dr. Harold Kaiser; Clinical Research Institute, Minneapolis, MN; Dr. John Cohn, Asthma Allergy & Pulmonary Associates, PC, Philadelphia, PA; Dr. Dennis Doherty, University of Kentucky Medical Center, Lexington, KY; Dr. Timothy Craig, Penn State Hershey Medical Center, Hershey, PA; Dr. Christopher Vanderneck, Meridian Clinical Research, Omaha, NE; Dr. Rebecca Gruchella, Utah Southwestern Medical School, Dallas, TX; Dr. Alan Reichman, Reichman & Associates, Sugarland, TX; Dr. Milan Slijvich; Allergy Clinic of Garland PA, Garland, TX; Dr. Michael Ruff, Pharmaceutical Research & Consulting, Inc, Dallas, TX; Dr. Mary Strek, University of Chicago, Chicago, IL; Dr. Peter Constantini, Atlantic Research Associates, Margate, NJ; Dr. Kathy Lampl, Asthma and Allergy Associates, Rockville, MD; Dr. Michael Spandorfer; Pulmonary & Critical Care Medicine, Charleston, SC; Dr. Robert Townley, Creighton University Center for Allergy, Asthma & Immunology, Omaha, NE; Dr. Rohit Patel, Pinnacle Research Group, LLC, Anniston, AL; Dr. Douglas Schumacher, Radiant Research Columbus, OH; Dr. Lawrence Gelber, Commonwealth Clinical Research Specialists, Richmond, VA; Dr. Donald Brandon, California Research Foundation, San Diego, CA; Dr. Robert Lapidus, Rocky Mountain Center for Clinical Research, Wheat Ridge, CO; Dr. David Schneider, Rx R&D, Metairie, LA; Dr. Bruce Prenner, Allergy Associates Medical Group, San Diego, CA; Dr. Steven Radwany, Akron Internists Research Foundation, Akron, OH; Dr. Robert Webb, Allergy and Asthma Research Associates, Kirkland, WA; Dr. Naomi Fieman, Mountain View Clinical Research, Denver, CO; Dr. Carlos deLaGarza, Unifour Medical Research, Hickory, NC; Dr. Meenashki Patel, Valley Medical Center, Centerville, OH; Dr. Edward Kent, Timber Lane Allergy and Asthma Research LLC, South Burlington, VT; Dr. Raul Laguarda, Charles River Medical Associates, Natick, MA; Dr. Eliot Dunsky, Philadelphia, PA; Dr. Irwin Spirn, Delaware Valley Clinical Research, Cherry Hill, NJ; Dr. Eugene Fletcher, University of Louisville, Louisville, KY; Dr. Imran Khawaja, Robin Ashford, Huntington, WV; Dr. Don McNeil; Optimed Research, LLC, Columbus, OH; Dr. Jonathan Matz, Atlantic Asthma and Allergy Center, Baltimore, MD; Dr. William Rees, PI-Coor Clinical Research, Burke, VA; Dr. Sooji Lee-Rugh, Millenium Clinical Research, LLC, Arlington, VA; Dr. Marcus Zervos, William Beaumont Hospital Royal Oak, MI; Dr. Patricia Buchanan, River Road Medical Group, Willamette Valley Clinical Studies, Eugene, OR; Dr. Tracy Green, Family Health Center, Sparks, NV; Dr. Jonathan Ilowite, Winthrop University Hospital Pulmonary Associates, Mineola, NY; Dr. John Behm, Northern Area Family Medicine, Pittsburgh, PA; Dr. Ronald H. Saff, Allergy & Asthma Diagnostic Treatment Center, Tallahassee, FL; Dr. David Brown, Mountain Allergy & Asthma, Asheville, NC; Dr. Jean-Claude Labissiere, Essex Medical Associates, Orange, NJ; Dr. Arnold Funkes, Alta Clinical Research, LLC, Tucson, AZ; Dr. William Massey, Pulmonary Associates of the Southeast, PC, Birmingham, AL; Dr. Frederick Kahn, Montana Health Research, Billings, MT; Dr. Alan Heller, San Jose Clinical Research, San Jose, CA; Dr. Richard Castaldo, Private Practice, Tonowanda, NY; Dr. Russell Leftwich, Nashville Asthma & Allergy, Nashville, TN; Dr. Selwyn Spangenthal, Charlotte Lung and Health, Charlotte, NC; Dr. Angelo Sparagna, Atlantic Research Associates, Margate, NJ; Dr. Jeffrey Glassheim, Fresno, CA; Dr. Michael Brown, Crescent Clinical Research, Inc., Pensacola, FL; Dr. Lauro Roberto, Children's Hospital Central California, Madera, CA; Dr. David Gross; Ntouch Research, Washington, DC; Dr. Richard White, University of California Davis, General Medicine Investigative Clinic, Sacramento, CA; Dr. George Bensch, Bensch Clinical Research Associates; Stockton, CA; Dr. Richard Weiss, Medical Research Unlimited, Hialeah, FL; Dr. Matthew Hegewald, Bend Memorial Clinic, Bend, OR; Dr. Andres Redondo, CliniTrials, Miami, FL; Dr. David Hugh Frazer, Drug Research and Analysis Corporation, Montgomery, AL; Dr. Joel Porter; IHC Health Center, Layton, UT; Dr. Thomas M. Hyers, CAR.E. Clinical Research, St. Louis, MO; Dr. Jatin J. Kadakia, Access Clinical Trials, Inc., Clarksville, TN; Dr. Jon K. Van Valkenburg, Medford Medical Clinic, Medford, OR; Dr. Alan Nolasco, MediClinic, Houston, TX; Dr. Shull Lemire, Northwest Physicians Research Network, Inc., Missoula, MT; Dr. Ricardo Tan, California Allergy & Asthma Medical Group, Palmdale, CA; Dr. James McFeely, Berkeley Pulmonary Medical Group, Berkeley, CA; Dr. David G. Hill, Waterbury Pulmonary Associates, Waterbury, CT; Dr. Richard Mangi, Allergy, Arthritis and Infectious Disease Associates, Hamden, CT; Dr. Bobby Lanier; North Texas Institute for Clinical Trials; Fort Worth, TX; Dr. David Bouda, Heartland Clinical Research, Inc., Omaha, NE; Dr. John. Murray, ASAP Research, Nashville, TN; Dr. Bharat Latthe, North Belt East Medical Clinic, PA, Houston, TX; Dr. Reynold Karr, Physicians Pharmaceutical Study Services, Everett, WA; Dr. Constantine Saadeh, Amarillo Center for Clinical Research, Ltd.; Amarillo, TX; Dr. Kevin Schaffer, Allergy & Asthma Clinical Research Center, LLC, Lawrenceville, GA; Dr. Jonathan Corren, Allergy Research Foundation, Los Angeles, CA; Dr. Susheela Bala, Allergy & Asthma Clinic, San Bernardino, CA; Dr. Gregory Lux, St John's Medical Research, Springfield, MO; Dr. Stephen Pollard, Family Asthma & Allergy Research Institute, Louisville, KY; Dr. Kajori Thusu, Universal Biopharma Research Inc., Dinuba, CA; Dr. Ashok Patel, Academy Allergy, Asthma & Immunology, Pueblo, CO; Dr. Alan Bakst, Medical Specialists of Palm Beaches, Inc., Boynton Beach, FL; Dr. David Cardona, Universal Biopharma Research Inc., Fresno, CA; Dr. Shams Iqbal, Asthma & Allergy Group, Riverside, CA; Dr. Jimmie Tarro, Allergy Asthma & Dermatology Research Center, LLC, Lake Oswego, OR; Dr. Eugene Bleecker, Cloverdale Research Facility, Winston Salem, NC; Dr. John Oppenheimer, Pulmonary & Allergy Associates, Springfield, NJ; Dr. John F. Pinto, Clinical Research Center of Nevada, Las Vegas, NV; Dr. June Hawkins, Asthma Allergy Center, Tigard, OR; Dr. Jan Westerman, Private Practice, Jasper, AL; Dr. A. Lynne Brannen, University Medical Associates, LLP, Augusta, GA; Dr. James Good, South Denver Pulmonary Associates, PC, Englewood, CO; Dr. Stephen H. Kimura, MED3000 Clinical Solutions Inc., Pensacola, FL; Dr.

Pinkus Goldberg; Clinical Research Center of Indiana, Indianapolis, IN; Dr. Robert Gao, Advanced Practice Clinical Research, Las Vegas, NV; Dr. Vicente Chavarria, Lovelace Scientific Resources; Miami, FL; Dr. Rachakonda Prabhu, Redrock Research Center, Las Vegas, NV; Dr. Terence T. Hart, Muscle Shoals, AL; Dr. Robert Webb, Yakima Chest Clinic PC, Yakima, WA; Dr. Dennis K. Ledford, University of South Florida Asthma, Allergy, Immunology, Tampa, FL; Dr. Jay K. Udani, Pacific West Research Corporation, Northridge, CA; Dr. Gary A. Cohen, Allergy and Asthma Prevention and Treatment Center, San Diego, CA; Dr. Allen Segal, Allergy Associates Research, Dallas, TX; Dr. Phillip Korenblat; The Clinical Research Center, LLC, St. Louis, MO; Dr. Aftab Naz, Madera Family Medical Group, Madera, CA; Dr. Elizabeth Gallup, Radiant Research, Overland Park, KS; Dr. Leon Greos, Colorado Allergy & Asthma Centers, PC, Englewood, CO; Dr. David Pearlman, Colorado Allergy and Asthma Centers, P.C., Denver, CO; Dr. Thomas Littlejohn, Piedmont Medical Research Associates, Winston Salem, NC; Dr. Edward Peters; Radiant Research, Austin, TX; Dr. Steven Weinstein, Allergy and Asthma Specialists Medical Group and Research Center, Huntington Beach, CA; Dr. Edward LeDoux, Pulmonary Consultants, PLLC, Tacoma, WA; Dr. Edward Kent, Timber Lane Allergy & Asthma, South Burlington, VT; Dr. Grant Olson, Colorado Allergy & Asthma Centers, PC, Lakewood, CO; Dr. Nathan Schultz, Allergy & Asthma Medical Group, Walnut Creek, CA; Dr. Stephen C. Ulrich, Pharmacotherapy Research Associates, Inc., Zanesville, OH; Dr. Andrew Pedinoff, Princeton Center for Clinical Research, Princeton, NJ; Dr. Harold Nelson, National Jewish Medical and Research Center, Denver, CO; Dr. Robert Berkowitz, Rx Research, Woodstock, GA; Dr. Jonathan Bernstein, Bernstein Clinical Research Center, LLC, Cincinnati, OH; Dr. Anjuli Nayak and Dr. Nicholas Nayak, Sneeze, Wheeze & Itch Associates, LLC, Normal, IL; Dr. Linda Ford, The Asthma and Allergy Center, Papillion, NE; Dr. David Levin, VAMC, Oklahoma City, OK; and Dr. Michael Blumberg, VA Adult & Pediatric Allergy & Asthma, Richmond, VA.

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Onset and Duration of Action of Formoterol and Tiotropium in Patients with Moderate to Severe COPD

Kai Richter[a] Stephan Stenglein[b] Marion Mücke[a] Christian Sieder[b]
Sören Schmidtmann[c] Ulf Harnest[d] Gottfried Weidinger[b]
Helgo Magnussen[a]

[a]Pulmonary Research Institute, Grosshansdorf, [b]Novartis Pharma GmbH, Nürnberg,
[c]Pulmologische Praxis, Berlin, and [d]Clinguard GmbH, Berlin, Germany

For editorial comment see p. 410

Key Words
Formoterol · Tiotropium · Bronchodilation · Chronic obstructive pulmonary disease

Abstract
Background: Chronic obstructive pulmonary disease (COPD) management guidelines recommend regular treatment with one or more long-acting bronchodilators for patients with moderate to severe COPD. ***Objective:*** To compare the onset and duration of action of formoterol and tiotropium in patients with COPD. ***Methods:*** This randomized, multicentre, open-label crossover study in 38 patients with COPD (mean age 64 years; mean FEV_1 55% predicted) assessed the effect of 7 days of treatment with formoterol (12 μg b.i.d. via Foradil® Aerolizer®) vs. tiotropium (18 μg o.d. via Spiriva® HandiHaler®) on lung function measured over a period of 12 h after the first dose on day 1 and the last dose on day 8. ***Results:*** The primary efficacy variable, FEV_1-AUC during the first 2 h post-dose (FEV_1-$AUC_{10-120\ min}$), was significantly higher for formoterol compared with tiotropium, with between-treatment differences of 124 ml ($p = 0.016$) after the first dose and 80 ml ($p = 0.036$) after 7 days' treatment in favour of formoterol. FEV_1 measured 12 h after inhalation did not differ statistically significantly between treatments. Adverse events occurred in 2 (5%) patients after treatment with formoterol and in 5 (12%) patients after treatment with tiotropium. ***Conclusion:*** This study demonstrates faster onset of action and greater bronchodilation of formoterol vs. tiotropium for bronchodilation within the first 2 h of inhalation (FEV_1-$AUC_{10-120\ min}$) and comparable bronchodilation 12 h post-inhalation in patients with moderate to severe COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is, according to the definition of the American Thoracic Society (ATS), a disease with abnormal expiratory flow. The airway obstruction is caused not only by inflammation, but also as a result of structural changes of the lung parenchyma.

Therapeutic guidelines are provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1]. These guidelines recommend the treatment of airflow obstruction with bronchodilators, including short- or long-acting β_2-agonists, anticholinergics, and methylxanthines.

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Dr. Kai Richter
Pulmonary Research Institute at Hospital Grosshansdorf
Center for Pneumology and Thoracic Surgery
Woehrendamm 80, DE–22927 Grosshansdorf (Germany)
Tel. +49 4102 601 390, Fax +49 4102 601 379, E-Mail k.richter@pulmoresearch.de

The most important bronchodilators for treatment of COPD at present are β_2-agonists and anticholinergics. Formoterol has a fast onset of action, in both asthma [2, 3] and COPD [4], with a 12-hour effect on spirometry [5, 6]. Studies with the long-acting anticholinergic compound tiotropium demonstrated that an 18-μg dose is safe and provides effective bronchodilation suitable for maintenance therapy in COPD with once-daily dosing [7–10].

An in-vitro study has shown a slower onset of action for tiotropium as compared with atropine or ipratropium bromide in guinea pig and human airways, with times required to attain 50% of the maximum response of 35 min compared to 4 and 8 min, respectively [11]. In a previous study comparing the pharmacodynamic properties of tiotropium with ipratropium in patients with COPD, tiotropium produced a peak increase in forced expiratory volume in 1 s (FEV_1) 3–4 h after dosing as compared with 1–2 h for ipratropium [12]. From a therapeutic standpoint it is useful to know the onset of bronchodilator response for agents used in COPD treatment (e.g. improvement in lung function, reduced symptoms, and increased exercise tolerance). Maesen et al. [13] were able to show that patients' subjective perception of the onset of bronchodilation matched objective clinical measurements of the onset of bronchodilation.

Few data are available on direct comparisons of the bronchodilation attributed to tiotropium and formoterol or to the combination of both drugs in patients with COPD [14–16]. The aim of this study was to compare the onset, duration of action, and lung function after the first dose and after 7 days of treatment with formoterol 12 μg twice daily (b.i.d.) or tiotropium 18 μg once daily (o.d.) in patients with moderate to severe COPD.

Methods

Patients

Forty patients (male, n = 31) >45 years of age with an established clinical history of COPD according to ATS criteria [17] were enrolled into the study. Inclusion criteria included an FEV_1 of 30–80% of predicted value and a FEV_1/forced vital capacity (FVC) ratio below 70% of the predicted value at screening. Additionally, all patients had a smoking history of at least 10 pack-years. Use of oral corticosteroids, theophylline or other xanthine derivatives, inhaled anticholinergics, oral or inhaled long-acting β_2-agonists was not permitted during the study period. Patients with respiratory tract infections occurring within 1 month before screening or with hospitalization due to a COPD exacerbation within 1 month before screening and during the screening phase were also excluded.

Therapy with ICS was allowed in a constant dose. Salbutamol was used as rescue medication. Demographics and baseline characteristics of enrolled patients are given in table 1.

Table 1. Demographics and baseline characteristics of the randomized patients (n = 40)

Age, years	64 ± 7
Males:females	31:9
Height, cm	171 ± 7
Weight, kg	78 ± 12
Smoking history, pack-years	44 ± 24
Current smoker, yes:no	16:24
FEV_1, ml	1,620 ± 450
FEV_1, % predicted	55 ± 12
FEV_1, reversibility % baseline	15.3 ± 14.4
FVC, ml	2,960 ± 700
FEV_1/FVC, %	55 ± 10
Pre-study medication for COPD, patients, n (%)	
Anticholinergics	5 (13)
β_2-Agonists inhaled	32 (80)
Inhaled steroids	14 (35)
Oral steroids	0

Study Design

The study followed an open-label, randomized, multicentre, two-period crossover design. The study was approved by an independent ethics committee and all patients gave informed and written consent to participate in the study prior to enrolment. The trial was carried out in accordance with the German drug law and principles of the Declaration of Helsinki.

Patients were randomly assigned to receive either formoterol 12 μg b.i.d or tiotropium 18 μg o.d. or to receive the same treatments in the reverse order. Tiotropium was administered via the HandiHaler® and formoterol was administered via the Aerolizer®; both devices are dry powder inhalers.

Each treatment phase lasted for 7 days with a washout period of 7 ± 2 days between treatments. Lung function measurements were performed after the first dose (days 1 and 15) and after the last dose (days 8 and 23) of each treatment period at approximately the same time of the day (between 08:00 and 10:00 h).

Measurements

The primary efficacy variable, FEV_1, was measured 10, 20, 40, 60, 90 and 120 min after inhaling the study medication in the morning on days 1, 8, 15, and 23. FEV_1 was measured using an electronic pneumotachograph MasterScope Model 4.1 spirometer (Fa. Jaeger, Hoechberg, Germany) according to the ATS recommendations [18]. FEV_1 was measured at least 3 times until reproducible within 5%; the highest value was used for the analyses. FEV_1 was also measured over 12 h at 3, 4, 6, 9, and 12 h after inhaling the study medication on days 1, 8, 15, and 23.

FEV_1, forced inspiratory volume in 1 s (FIV_1), inspiratory capacity (IC), and inspiratory vital capacity (IVC) as trough values were the secondary variables and were evaluated before inhaling the study medication on days 1 and 8 and on days 15 and 23.

Morning and evening peak expiratory flow (PEF) and clinical symptoms including cough, sputum, awakening in the night and breathing effort were recorded daily in patient diaries. The number of inhalations of rescue medication (salbutamol) was reported dai-

Table 2. Results of differences of area under the curve (AUC) for time course of FEV_1

	After first dose (day 1/15) formoterol vs. tiotropium	p value	After last dose (day 8/23) formoterol vs. tiotropium	p value
ITT population (n = 38)				
10–120 min	+114 ml (24/204 ml)	0.014	+82 ml (14/150 ml)	0.020
0–720 min	+61 ml (–26/148 ml)	0.165	+3 ml (–52/58 ml)	0.920
PP population (n = 34)				
10–120 min	+124 ml (25/223 ml)	0.016	+80 ml (6/154 ml)	0.036
0–720 min	+52 ml (–44/149 ml)	0.279	+6 ml (–42/64 ml)	0.828

Values are given as means (95% confidence intervals). AUC values are standardized by observation time in min.

ly in the morning and in the evening after inhalation of the study medication and was also recorded in patient diaries.

Exercise tolerance was measured by a 6-min walking test [19] at the screening visit and on days 8 and 23 of the respective treatment periods before inhalation of the study drug. Reversibility of lung function impairment was tested at screening after inhalation of salbutamol 200 μg in terms of maximal increase of FEV_1 in percent of baseline after 15 min.

Patient perception of dyspnoea was assessed by Baseline Dyspnoea Index (BDI) [20] at the screening visit and on days 8 and 23 of the respective treatment periods by Transition Dyspnoea Index (TDI) before inhalation of the study drug.

Safety Assessments

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events (with their severity and relationship to study drug), the monitoring of haematology and blood chemistry and assessments of vital signs, ECG and body temperature.

Statistical Analysis

Area under the curve (AUC) was calculated for FEV_1 for the time interval 10–120 min (primary efficacy variable) and 0–12 h (secondary efficacy variable) and normalized according to the corresponding observational period of 110 min and 12 h, respectively. The statistical analysis was performed by means of ANOVA. The differences in AUC were analysed for the ITT population and the per-protocol population.

The analysis of the additional secondary target variables was performed analogously, applying the same statistical model of ANOVA.

Assuming a difference in FEV_1-AUC of 100 ml between the two treatments and a within-patient standard deviation of about 230 ml, a sample size of 35 patients was required to demonstrate a superiority of formoterol on a one-sided α level of 5% and with 80% power.

Results

A total of 40 patients were screened and randomized into the study. Two patients terminated the study prematurely: 1 patient due to an adverse event, and 1 patient due to administrative reasons. The ITT population consisted therefore of 38 patients. Efficacy results are given for the ITT population if not stated otherwise. An additional evaluation of the primary efficacy variable was performed for the per-protocol group consisting of all patients who received study medication during the whole treatment phase and had no major protocol violations (34 patients).

Efficacy Results

FEV_1-$AUC_{10–120\,min}$ at the first visit of each treatment phase (days 1 and 15) after first dose and at the last visit of each treatment phase in the morning after the last dose (days 8 and 23) was statistically significantly greater at every visit after treatment with formoterol than after treatment with tiotropium.

The differences in the AUC between patients under treatment with formoterol and the same patients under treatment with tiotropium are given for the ITT and the per-protocol populations in table 2.

In the ITT population, the FEV_1-$AUC_{0–12\,h}$ after the first dose (days 1 and 15) and after the last dose (days 8 and 23) of treatment with formoterol exceeded the AUC after treatment with tiotropium by 61 and 3 ml, respectively. In the per-protocol group the differences were 52 and 6 ml, respectively. None of these differences was statistically significant.

The increase in FEV_1 3–6 h after inhalation of study medication was greater for patients receiving formoterol;

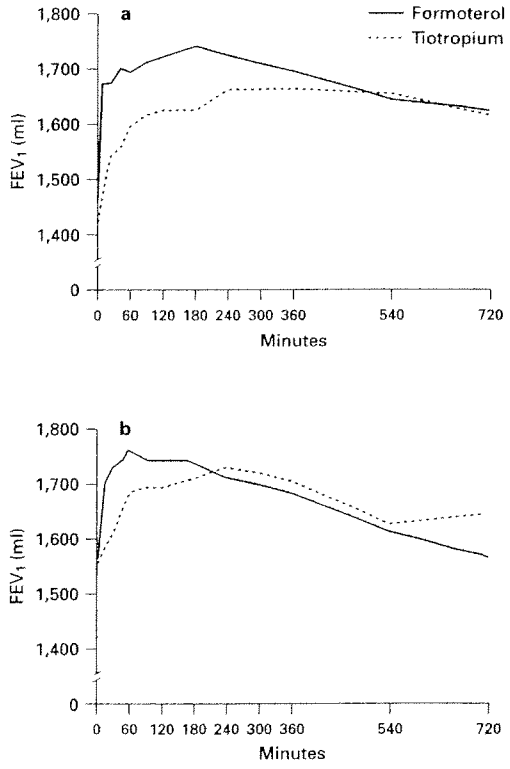

Fig. 1. 12-hour FEV_1 profiles after the first dose (days 1, 15) (**a**) and last dose after 7 days of treatment (days 8, 23) (**b**) of formoterol or tiotropium.

after this time point the course of the curves was similar for both treatment groups (fig. 1). The bronchodilation response as measured by FEV_1 over 12 h provided by formoterol and tiotropium is shown in figure 1.

Patients' perception of dyspnoea measured by BDI/TDI improved in both treatment groups to a similar extent. The sum score on days 8 and 23 after treatment with formoterol was 2.6 compared with 2.4 after treatment with tiotropium.

The mean distance covered during the walking test improved by 14.6 m after treatment with formoterol and by 10.1 m after treatment with tiotropium. The difference was not statistically significant. Rescue medication use of salbutamol doses decreased for both treatments, without statistically significant differences. No differences in clinical symptoms as recorded by patients were observed.

The results of an additional per-protocol analysis for the primary efficacy variable were consistent with those obtained in the ITT population.

Analyses of $AUC_{0-720\,min}$ of expiratory lung function variables (PEF, VC and FVC) showed small, statistically non-significant differences in favour of formoterol after the first dose, but not after dosing over 7 days. For inspiratory variables (FIV, IVC) also, a small difference in favour of formoterol after the first dose was observed.

Differences of $AUC_{0-720\,min}$ values of intrathoracic gas volume (ITGV), residual volume (RV) and total lung capacity (TLC) indicated less static lung hyperinflation after treatment with formoterol, but none of these differences reached statistical significance and they were smaller after repeated dosing. Data on lung function variables are provided in table 3.

Considering the treatment sequences, significant differences between the groups formoterol/tiotropium and tiotropium/formoterol were observed for all variables. Patients receiving formoterol in the first treatment phase had higher FEV_1 values at all measurement time points and in both treatment phases.

Safety Results

Eight patients (20%) experienced 11 adverse events during the study. During formoterol treatment, 3 adverse events occurred in 2 (5%) patients; during treatment with tiotropium, 6 adverse events occurred in 5 (12.5%) patients. Two adverse events in 1 (2.5%) patient occurred during the washout period. The most frequent adverse event was headache.

One serious adverse event occurred during the study. A patient with a history of hypertension and aortic insufficiency experienced apoplexy during treatment with tiotropium and terminated the study prematurely. This event was not deemed study drug related by the investigator.

Discussion

The results of this study suggest that formoterol is more efficacious than tiotropium in bronchodilation (FEV_1-$AUC_{10-120\,min}$) within the first 2 h after study drug inhalation. Both substances improved lung function variables and differences in duration of effect up to 12 h were not evident. These data are in line with previous studies showing the long duration of action of tiotropium and formoterol for at least 12 h [5, 6, 8].

Table 3. Results of differences of area under the curve ($AUC_{0-720\,min}$) for different lung function parameters after first and last dose

	After first dose (day 1/15) formoterol vs. tiotropium	p value	After last dose (day 8/23) formoterol vs. tiotropium	p value
PEF, ml/s	199 (–52/450)	0.12	–24 (–200/151)	0.78
VC, ml	59 (–80/198)	0.39	–51 (–131/30)	0.21
FVC, ml	70 (–67/207)	0.31	–30 (–119/60)	0.51
FIV_1, ml	76 (–65/207)	0.28	79 (–58/216)	0.25
IVC, ml	62 (–68/191)	0.34	–11 (–84/61)	0.75
IC, ml	–9 (–159/140)	0.90	108 (–76/294)	0.24
ITGV, ml	–105 (–244/35)	0.14	–58 (–216/101)	0.45
RV, ml	–108 (–298/83)	0.26	–20 (–206/166)	0.83
TLC, ml	–69 (–232/94)	0.40	–56 (–208/97)	0.46

All values are given as means (95% confidence intervals) standardized by observation time in minutes.
PEF = peak expiratory flow; VC = vital capacity; FVC = forced vital capacity; FIV_1 = forced inspiratory volume in 1 s; IVC = inspiratory vital capacity; IC = inspiratory capacity; ITGV = intrathoracic gas volume; RV = residual volume; TLC = total lung capacity.

In comparing two treatments it is important to evaluate not only the maximum increase in FEV_1, but also the time needed to achieve therapeutic effect. Patients treated with formoterol reached higher values of FEV_1 in a shorter period of time than patients treated with tiotropium, as demonstrated by the difference in FEV_1-$AUC_{10-120\,min}$. These differences were smaller after 7 days of treatment but still statistically significant in favour of formoterol. The fast onset of action of formoterol in COPD has been described in the literature [4, 16, 21] and was confirmed by the results of this study.

Analyses of secondary inspiratory and expiratory lung function variables did show small differences for $AUC_{0-720\,min}$ after the first dose in favour of formoterol but they did not reach statistical significance. In this regard the study is limited by the total number of subjects included, hence it was not adequately powered for exploring differences in these variables. Furthermore, it is known from previous studies that there is a rather poor correlation between FEV_1 and inspiratory lung function variables (e.g. FIV_1 or IC) or exercise capacity in COPD [22].

Significant differences between the treatment sequences formoterol/tiotropium and tiotropium/formoterol were observed for all variables. Patients in the formoterol/tiotropium sequence had higher FEV_1 values at all measurement time points and in both treatment phases. Additional analyses of lung function variables at screening indicated a less severe degree of disease for the patients of the formoterol/tiotropium sequence, therefore this imbalance does not indicate a carry-over effect. However, the advantage for formoterol existed in both treatment sequences. As the crossover design uses only within-patient comparisons, imbalances between treatment sequences do not invalidate the trial findings.

The pharmacologically induced bronchodilation in COPD might depend on the severity of disease (e.g. baseline lung function and degree of reversibility of airflow obstruction), which must be taken into account when comparing the efficacy of different β_2-agonists or anticholinergics. The crossover design of the present study comparing bronchodilation associated with formoterol and tiotropium within the same patient group may help reduce or eliminate such a bias. In this particular study partly reversible airflow obstruction was not an exclusion criterion. The population showed a mean reversibility of FEV_1 of about 15% at screening and included patients with partly reversible obstruction and patients with no reversibility. When comparing FEV_1 response to different bronchodilators in COPD, information about reversibility is important. The degree of reversibility might explain the clear response in terms of bronchodilation in this study. Nevertheless, inclusion and exclusion criteria ensured that only patients with COPD (and not asthma) entered the study. Hence the airflow obstruction was not fully reversible.

Bronchodilation provided by formoterol within the first 2 h was significantly higher than with tiotropium.

After 7 days of treatment this effect of formoterol was maintained, although the difference was much smaller. In a recent pharmacodynamic study on tiotropium, van Noord et al. [12] demonstrated that the steady state for bronchodilation in terms of FEV_1 is reached within 48 h while continued improvements in FVC may be expected beyond the first week of treatment with tiotropium. This effect of tiotropium on trough values might explain the smaller difference after 1 week of treatment in the current study. Therefore, the difference between formoterol and tiotropium in terms of onset of action and peak effect shown in this study might become less relevant with continuous treatment over a longer period of time.

In conclusion, this study has demonstrated that formoterol administered via the Aerolizer® is well tolerated and provides a higher degree of bronchodilation within the first 2 h and comparable bronchodilation over a period of 12 h compared with tiotropium with regard to improvement in FEV_1. These differences were maintained after treatment over 7 days and might have implications on future treatment of COPD with long-acting bronchodilators.

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ORIGINAL ARTICLE

A randomised, double-blind, placebo-controlled study to evaluate the role of formoterol in the management of acute asthma

Katayoon Najafizadeh, Hamid Sohrab Pour, Mojtaba Ghadyanee, Masoud Shiehmorteza, Masoud Jamali, Sayeed Majdzadeh

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See end of article for authors' affiliations

Correspondence to: Dr K Najafizadeh, Department of Pulmonary Medicine, National Research Institute of Tuberculosis and Lung Diseases, Tehran 19575/154, Iran; katynajafi@nritld.ac.ir

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Aim: To evaluate the efficacy and tolerability of formoterol delivered by Aerolizer in the emergency department.

Methods: A single-centre, double-blind, randomised, placebo-controlled, parallel group study was conducted in patients seeking emergent care for an acute exacerbation of asthma. Patients were randomly assigned to one of two groups: group 1 (salbutamol), receiving a total dose of 600 μg salbutamol (200+200+200) delivered by a meter-dose inhaler into a spacer device as two puffs at 20 min intervals; and group 2 (formoterol), receiving formoterol 24 μg (12+12) as two dry powder capsules each containing 12 μg of formoterol via Aerolizer at 20 min intervals. The peak expiratory flow rate (PEFR) was measured at baseline and 5 min after the second and third doses.

Results: 60 subjects receiving salbutamol (n = 28) or formoterol (n = 32) completed the study. Age, gender, baseline PEFR, duration of asthma and previous medication were balanced between the two groups. Mean PEFR increased significantly over baseline values in both the salbutamol and formoterol groups (63% in the salbutamol group, p = 0.001, and 55% in the formoterol group, p = 0.001). No significant difference was observed in the increase in PEFR between the groups (p = 0.99, 95% CI −29.62 to 29.59). The proportion of patients reporting adverse events was similar in the two groups.

Conclusion: Formoterol was found to be well tolerated and as effective as salbutamol in the management of acute asthma. Further studies are needed to follow the patients after discharge from the emergency room to compare the long-term effect of formoterol on patients' stability.

Despite the increasing use of long-acting β_2-agonists in clinical practice, relatively few studies have addressed their role in acute asthma.[1] β_2-agonists with long-acting properties, formoterol and salmeterol, are recommended only as maintenance therapy in patients with moderate to severe asthma that is poorly controlled on inhaled corticosteroids.[1 2] In addition to its use in maintenance therapy, formoterol is approved in Europe as a reliever medication. The National Heart, Lung, and Blood Institute, Maryland, USA emphasises that long-acting β_2-agonists should not be used to treat acute symptoms or exacerbations.[2]

Currently, the repetitive administration of short-acting inhaled β_2-agonists (2–4 puffs every 20 min for the first hour) is considered the preferred initial treatment for acute asthma.[3] Thereafter, the dose of β_2-agonist required will depend on the severity of exacerbation, and varies from 2 puffs every 3 h to 10 puffs at internals of less than an hour.[3]

The rationale for using long-acting β_2-agonists in the emergency department (ED) as a substitute to short-acting β_2-agonists relates to their duration of action and potential for reducing the need of repeated administration of bronchodilator therapy.[1]

Formoterol, a long-acting β_2-agonist with unique pharmacological properties as well as a favourable safety profile, seems ideal for the management of acute asthma. It has a fast onset of action, similar to that of short-acting β_2-agonists such as salbutamol. In all, 80–90% of maximum bronchodilation occurs within 5–10 min of inhalation.[4 5] An improvement in the mean forced expiratory volume in one second is sustained over 24 h after dosing, although the clinical duration of action is reported to be 12 h.[6 7] In addition to rapid bronchodilation, the safety and tolerability high-dose formoterol Turbuhaler relative to high-dose terbutaline Turbuhaler and salbutamol meter-dose inhaler (MDI) in the treatment of asthma exacerbation has been confirmed by previous comparative and non-comparative studies.[8 9]

Formoterol is equally effective when given either by Aerolizer or by Turbuhaler.[10 11] However, handling the Aerolizer is easier than handling the Turbuhaler, and patients make less critical errors while using an Aerolizer than while using a Turbuhaler.[12 13] This feature could be especially valuable in choosing an alternative treatment for asthma exacerbation.

A recent study shows that rapid onset of bronchodilation can be achieved by administering formoterol via Turbuhaler (Oxis, Astrazeneca, Sweden) in patients with asthma exacerbation, which is associated with greater maximal efficacy during the third and fourth hour after dosing compared with salbutamol administered via MDI. In addition, it provides a safety profile at least as good as that of salbutamol when used up to 54 μg.[9]

Although the efficacy and safety of high-dose formoterol delivered by Turbuhaler in asthma exacerbation has been demonstrated, that of low-dose formoterol delivered by Aerolizer has not yet been studied.

The present study compares the efficacy and tolerability of equipotent doses of formoterol delivered by Aerolizer with that of salbutamol delivered by MDI.

METHODS

Study population

We recruited adult patients with acute asthma over a 3-month period. These patients had approached the ED of "Shaheed

Abbreviations: AE, adverse event; ED, emergency department; MDI, meter-dose inhaler; PEFR, peak expiratory flow rate

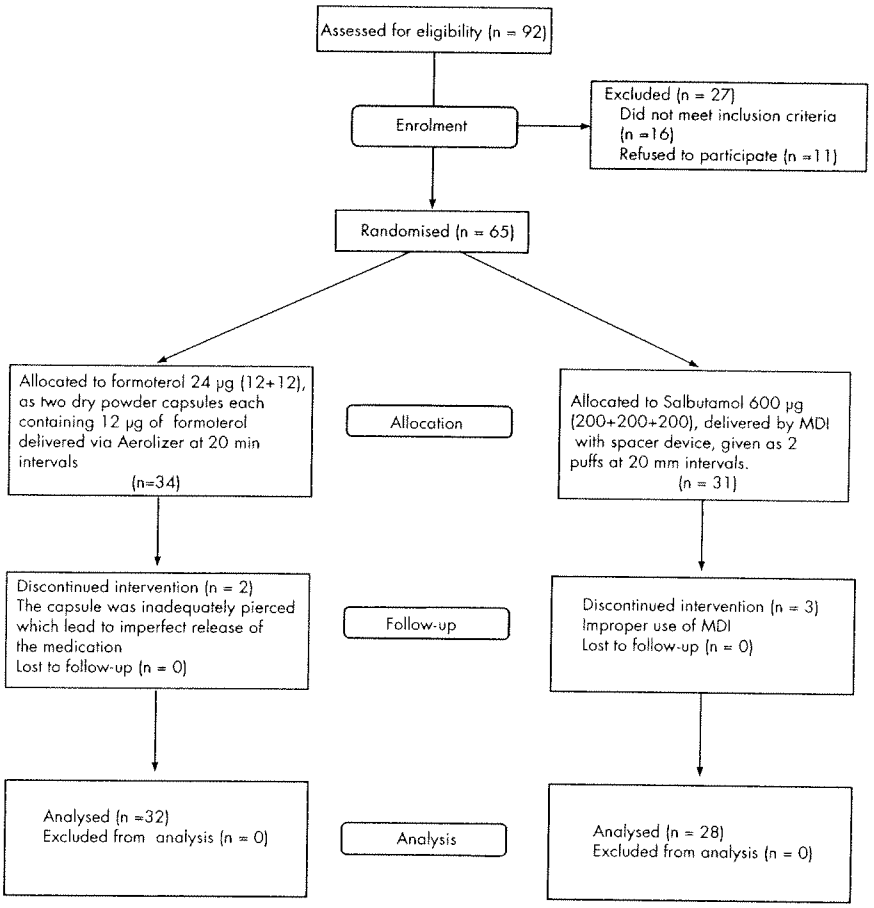

Figure 1 Flow chart describing the progress of patients through randomised trial.

Labafinejad" hospital, Tehran, Iran. Approximately 22 000 patients visit this department annually, with nearly 1400 adult patients presenting with asthma exacerbation.

To be included in the study, patients had to fulfill the following criteria:

- Age >18 years
- American Thoracic Society's definition of asthma[14]
- No history of hypersensitivity to β_2-agonists, thyrotoxicosis, ischaemic heart disease; severe tachyarrhythmia, heart failure, uncontrolled hypertension, pregnancy or breastfeeding
- Able to perform a forced expiratory manoeuvre.

All patients with severe life-threatening acute asthma who required admission to the intensive care unit were excluded from the study.

The study was approved by the medical ethics committee of the Shaheed Beheshti University of Medical Sciences, and Health Services and informed consent was obtained from all patients.

Study design

The study had a single-centre, double-blind, randomised, parallel-group design. Demographic data, duration of asthma and treatment given at arrival to the ED were recorded.

The eligible patients were assigned by random number allocation to one of the two treatment groups—that is, either salbutamol or formoterol. Randomisation was carried out using sequential opaque sealed envelopes in which treatment allocation had been predetermined using blocked randomisation by a statistician not related to the study. Both treatments were started as soon as possible after the patient's arrival at the hospital.

In the salbutamol group, a total dose of 600 µg salbutamol (200+200+200) delivered by MDI with a spacer device (Jahan-Behbood, Tehran, Iran) was given as two puffs (100 µg/puff) at 20-min intervals. Patients in the second group were given formoterol 24 µg (12+12) as two dry powder capsules each containing 12 µg of formoterol via Aerolizer (Novartis Pharma AG, Basel, Switzerland) at 20 min intervals. The drugs were administered in a double-blind manner. As placebo, the patients in the salbutamol group received two dry powder capsules, containing lactose, at the first and second doses in addition to salbutamol. The safety of lactose has been proven by previous studies.[15]

Patients in the formoterol group received two puffs from an identical MDI placebo (Jahan-Behbood) at 20 min intervals concurrently. All treatments were administered by ED nurses who were trained to use the inhaler and were unaware of the treatment groups.

To omit the effect of other drugs on our outcome, systemic corticosteroids were added only to the treatment of those patients who did not respond to the third dose of the drug under study.

The decision to discharge or admit a patient was made by the ED attendant physician, who did not have any knowledge of

the patient group allocation. Patients were discharged from the ED according to the British Thoracic Society guidelines[16] and if they were improving clinically. All discharged patients were given prednisolone 60 mg daily for at least 5 days.

Measurements

The primary efficacy parameter was PEFR. It was measured with a peak flow meter (Jaeger, Germany) immediately before starting the treatment and 5 min after the second and third doses. At each assessment, the highest PEFR value was recorded from three manoeuvres. As self-recording of PEFR by the patients themselves might be inaccurate, four ED nurses who were trained to use a peak flow meter performed all the measurements. After completing the full dose, patients were asked to indicate the presence or absence of each of the following symptoms: mouth dryness, dizziness, headache, nausea, palpitation, tremor and cramps. Secondary efficacy parameters included: proportion of patients who required hospitalisation, and proportion of patients who needed additional medication after completing the full dose of β_2-agonists.

Statistical methods

Differences in mean PEFR between the two groups were analysed by applying the Student's t test. Paired t test was used to compare PEFR before and after the second and third administrations to determine whether there were significant improvements in either group.

A previous trial has reported that the mean PEFR in persons with asthma exacerbation treated by salbutamol was 227.1 l/min, with a SD of 71.7 l/min.[17] Estimations from power calculations predicted that 29 patients in each group (salbutamol and formoterol) would be required to detect a difference of 55 l/min in mean PEFR between the two treatment groups, at α (two-sided) = 0.05 and power = 80%.

The proportion of patients who required hospitalisation or additional medication after the full dose of β_2-agonists was compared using the x^2 test.

RESULTS

Demographics and baseline characteristics

From a total of 92 patients enrolled in the study, 65 patients were randomised to treatment with either salbutamol or formoterol: 34 in the formoterol group and 31 in the salbutamol group. Figure 1 shows the progression of patients through the study phases. A total of five patients discontinued the study: 2 (6.25%) patients from the formoterol group (due to inadequate piercing of the capsule, which led to imperfect release of the medication) and 3 (9.6%) patients from the salbutamol group (due to improper use of MDI).

Table 1 shows the demographic characteristics of the 60 patients who completed the study, and their baseline PEFR. The two treatment groups were well matched with regard to demographic characteristics. The mean PEFR value at baseline in the formoterol group (119.3 l/min) was higher than that in the salbutamol group (100.8 l/min). However, the difference was not statistically significant. A similar number of patients in each group had taken asthma medication. Of the 60 patients, 58 (96.7%) used inhaled β_2-agonists (salbutamol), 23 (38.3%) used inhaled glucocorticosteroids, 43 (71.7%) used theophylline, 30 (50%) used systemic glucocorticosteroids and 4 (6.7%) used cromolyn as previous medication.

Table 1 Baseline characteristics of the two treatment groups

Variables	Salbutamol (n = 28)	Formoterol (n = 32)
Sex (M/F)	14/18	13/15
Age (years), mean (SD)	53.2 (15.0)	56.4 (14.2)
Duration of asthma (years), mean (SD)	12.4 (8.4)	10.4 (8.1)
PEFR at baseline (l/min)	100.8	119.3

F, female; M, male; PEFR, peak expiratory flow rate.

Efficacy results

In both groups, PEFR increased significantly over baseline values. Overall, there was no significant difference in mean PEFR changes after the third dose of treatment between the two groups (65.9 l/min in the salbutamol group vs 65.9 l/min in the formoterol group, p = 0.99, 95% CI, −29.62 to 29.59; table 2).

Among the treatment groups, there were no statistically significant differences in the need for additional drugs or hospitalisation.

In all, 9 (28.1%) patients of the formoterol group and 9 (32.1%) patients of the salbutamol group needed an additional drug such as corticosteroids for the control of their exacerbation. In addition, 4 (12.5%) in the formoterol group and 5 (17.8%) in the salbutamol group required hospitalisation and were admitted.

Adverse events

Both treatments were well tolerated, and no unusual or unexpected adverse events (AEs) were reported. Overall, 34 AEs were reported. Typical β_2-receptor-mediated subjective symptoms (reported as AEs) occurred during treatment with formoterol in 12 (43%) patients and during treatment with salbutamol in 11 (42.9%) patients. The most common AE was mouth dryness in 22 (36.7%) patients, which occurred with similar frequency in both groups. There were no differences in the formoterol and salbutamol groups with regard to reporting AEs (table 3).

DISCUSSION

We compared the efficacy and tolerability of the two treatment regimens (formoterol 24 μg as two dry powder capsules each containing 12 μg of formoterol via Aerolizer and salbutamol 600 μg via MDI with spacer in three equal doses) in providing relief of acute asthma exacerbation in the ED setting.

The results from this study demonstrated that formoterol delivered by Aerolizer was at least as effective as salbutamol delivered by MDI, based on improvement in PEFR at 5 min after the second and third doses in patients with acute asthma exacerbation.

Both formoterol Aerolizer and salbutamol MDI improved PEFR, and the difference between treatment groups for change in PEFR value from baseline to post second and third doses was not significant.

Table 2 Improvement in peak expiratory flow rate (l/min) after the second and third doses compared with baseline

PEFR	Salbutamol (n = 28)	Formoterol (n = 32)	p Value
Baseline–second dose	40.5 (22.5 to 58.5)	47.3 (32.1 to 62.5)	0.55
Baseline–third dose	65.9 (41.2 to 90.5)	65.9 (47.4 to 84.4)	0.99
Second–third dose	25.3 (14.9 to 35.8)	18.5 (7.7 to 29.4)	0.36

PEFR, peak expiratory flow rate.
All p values are for two-tailed t tests.
Values in parentheses are 95% CI.

Table 3 All important adverse events or side effects in each intervention group

Symptoms	Formoterol group n (%)	Salbutamol group n (%)	p Value
Mouth dryness	12 (37.5)	10 (35.7)	NS
Dizziness	5 (15.6)	2 (7.1)	NS
Headache	3 (9.4)	2 (7.1)	NS

Furthermore, the rapid onset of action of formoterol Aerolizer in asthma exacerbation was in accordance with previous studies.[6 7]

The rapid onset of action of formoterol and salbutamol is explained by the ability of these drugs to reach the β_2-adrenoceptor from the aqueous phase, but, unlike salbutamol, formoterol is moderately lipophilic, enabling a considerable amount of drug, when inhaled, to diffuse into the lipid bilayer and to produce a long duration of action.[18 19]

This is the first study to compare formoterol Aerolizer and salbutamol MDI in asthma exacerbation. Boonsawat *et al*[9] compared the efficacy and safety of high-dose formoterol delivered by Turbuhaler with that of salbutamol delivered by MDI. Considering the fact that formoterol induces bronchodilation in a dose-dependent manner,[20 21] there would be a concern that a lower dose of formoterol could not be used in the management of acute asthma. Our results further extend the findings of this study to the effectiveness of a lower dose of formoterol in a population with asthma having more severe obstruction of airways.

Previous studies suggest that formoterol 12 μg Aerolizer is an equivalent bronchodilation dose to salbutamol 200 μg MDI.[6] On the basis of the Global Initiative for Asthma guideline for the treatment of asthma exacerbation, which recommends two to four puffs of short-acting β_2-agonist every 20 min for the first hour,[3] we decided to compare formoterol Aerolizer with the lowest recommended dose of salbutamol.

In addition, patients with forced expiratory volume in one second <30% of predicted normal value were excluded in Boonsawat *et al*'s[9] study. Therefore, the study population did not represent the severe end of the spectrum of asthma exacerbation. However, in our study, any patient with asthma exacerbation who was able to generate a PEFR value was enrolled.

Unlike previous trials, the mean baseline PEFR value obtained in this study was very low in both groups (119.3 and 100.8 l/min), which was probably due to the age differences observed in these studies. The majority of our patients in both groups were aged >50 years, and this could have contributed to the lower mean PEFR value. In addition, our sample was drawn from a hospital which is a referral centre for patients with respiratory disorder with more severe forms of asthma exacerbation.

Given that our goal was to assess the role of formoterol in the management of asthma exacerbation, this low mean PEFR value did not seem to affect our results.

To manage asthma exacerbation in hospital, it is recommended that rapid-acting inhaled β2-agonists be administered via either MDI or a nebuliser. Current guidelines for the management of acute asthma, including The British Thoracic Society guidelines, have not mentioned that a nebuliser is superior to the MDI and spacer in treating mild and moderate exacerbations of asthma in children ≥2 years old and in adults.[22 23]

Owing to the improper usage of the inhaler devices by most patients in Iran, β2-agonists will be administered via an MDI by an appropriate volume spacer in hospital management of asthma exacerbation without life-threatening features. Our chronic asthma treatment is based exactly on the Global strategy for asthma management and prevention.[3]

In our study, 2 (6.3%) patients in the formoterol group and 3 (10.7%) patients in the salbutamol group experienced a decline or no change in PEFR after administration of the sprays. All of these patients except one patient in the salbutamol group who was hospitalised, had an improvement in their symptoms.

One possible explanation could be that the improvement in the patient's well-being has a mechanism different from the bronchodilatory and bronchoprotective effects of the β_2-agonists.

Another explanation could be related to the fact that each patient with asthma has a distinct number of β-receptors, which respond to individualised doses of β_2-agonists.[24]

Therefore, the dose used in our study might not have been sufficient enough for them.

The safety profile of formoterol is well established.[25] Several studies[26–28] have shown that, despite having a prolonged bronchodilator effect in the airways, formoterol has a short duration of systemic effects. The proportions of patients reporting AE in this study were similar in the two groups, but more than those observed in previous studies. Mouth dryness and dizziness were the most frequent AEs. Neither tremor nor palpitation developed in any of our patients in the salbutamol group. There were no serious AEs and no discontinuations due to AEs. Formoterol was well tolerated, with no unusual or unexpected AEs. Patients in this trial received a maximum of 24 μg of formoterol via dry-powder inhaler. We did not evaluate the cardiovascular and metabolic effects of this dose of formoterol in our patients. This dose was well within the tolerability range of formoterol, as evidence suggests that formoterol up to a daily dose of 120 μg delivered through Aerolizer has a safety profile comparable to that of short-acting β_2-agonists.[29]

Our results support prior studies in suggesting formoterol as a very useful bronchodilator and as a potential substitute for controlling acute asthma attack. Our study was limited by several factors.

First, we did not follow patients after being discharged from the ED. The long-term efficacy and safety of formoterol for management of asthma exacerbation needs to be assessed in future studies. We focused only on PEFR as the primary efficacy parameter in designing and implementing the study. The other data required for assessing the severity of asthma, such as respiratory rate, pulse or arterial blood gas results, were not included in this study, which could be another limitation. However, initial assessments (history, physical examination and tests) were performed for all patients according to the Global strategy for asthma management and prevention. Finally, the numbers enrolled were small, thus limiting our ability to detect smaller but potential clinically significant differences.

Authors' affiliations
Katayoon Najafizadeh, Masoud Shiehmorteza, Masoud Jamali, Department of Pulmonary Medicine, National Research Institute of Tuberculosis and Lung Diseases, Tehran, Iran
Hamid Sohrab Pour, Department of Pulmonary Medicine, Labbafinejad Hospital, Tehran, Iran
Mojtaba Ghadyanee, Department of Oncology, Taleghani Hospital, Tehran, Iran
Sayeed Majdzadeh, Department of Epidemiology, National Research Institute of Tuberculosis and Lung Diseases, Tehran, Iran

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